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EMA/CHMP/QWP/BWP/725078/2021

Overview of comments on the draft guideline on quality requirements for drug-device combinations (EMA/CHMP/QWP/BWP/259165/2019)

www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-requirements-drug-device-combinations_en.pdf

Comments from:

Stakeholder number	Name of organisation or individual
1	Respiratory group of the Spanish Society of Family and Community Pharmacy (SEFAC)
2	The International Primary Care Respiratory Group (IPCRG) Scotland - United Kingdom
3	Medicines for Europe
4	Association of the Austrian Pharmaceutical Industry (PHARMIG)
5	TEAM NB Article 117 Working Group
6	College ter Beoordeling van Geneesmiddelen – Dutch Medicines Evaluation Board
7	CarThera
8	PharmaLex GmbH
9	International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)
10	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
11	European Biosafety Network
12	European Industrial Gases Association (EIGA)
13	International Plasma and Fractionation Association (IPFA)
14	European Biopharmaceutical Enterprises (EBE) European Federation of Pharmaceutical Industries and Associations (EFPIA) Vaccines Europe (VE)
15	Acceleron Pharma, Inc.
16	Apotekarsocieteten (Swedish Pharmaceutical Society), Section for medicinal device
17	Regeneron Ireland D.A.C.
18	Medtech & Pharma Platform (MPP)
19	Mark Chipperfield, Corvus Device Ltd

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Stakeholder number	Name of organisation or individual
20	ACRO (Association of Clinical Research Organizations)
21	NextraResearch S.r.l.
22	Parenteral Drug Association (PDA)
23	Prescrire editorial team
24	BPI – German Pharmaceutical Industry Association
25	Medicoindustrien – The Danish Medical Device Industry
26	DBV Technologies
27	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)
28	Ferring Pharmaceuticals
29	Synthon B.V.
30	Pharmathen
31	MedTech Europe
32	Methra Uppsala AB/LSM group
33	Combination Products Coalition
34	Association of the European Self-Medication Industry (AESGP)
35	Chiesi Farmaceutici SpA
36	CSL BEHRING

1. General comments

Comment number	Stakeholder number	General comment	Outcome (if applicable)
1	1	It would be interesting if manufacturers were obliged to give placebos to educate or help the patient to use their devices (drug-device combinations) and if they were forced to give them to community pharmacists, hospital pharmacists, primary care doctors, specialist doctors and nurses.	The comment is acknowledged but is outside the scope of this guideline. No change is proposed.
2	2	<p>Instructions on inhaler</p> <p><i>Suggestions for change:</i></p> <p>Is it possible to have some instructions on the inhaler not just on the box or leaflet? Like "shake/don't shake", or "keep upright", "don't store in the bathroom" etc? Maybe with pictures? Having some minor instructions on the inhaler might improve use by patients.</p>	<p>The comment is acknowledged. Detailed QRD guidance is outside the scope of this guideline.</p> <p>The product information of integral medicinal products should follow the requirements of Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable (Quality Review of Documents templates).</p> <p>Information of the device (part) which is necessary for the intended use of the integral medicinal product should be included in the relevant sections of the package leaflet and SmPC, as applicable (for details refer to the SmPC guideline & the QRD annotated template).</p>
3	2	<p>Smart technology</p> <p><i>Suggestions for change:</i></p> <p>Given the rise of technology there are also smart applications to support these actions and also it is much easier to create videos adapted to local circumstances. There is no excuse for not creating a publicly video for each device.</p>	The comment is acknowledged but is outside the scope of this guideline. No change is proposed.
4	2	<p>Sustainability</p> <p><i>Comments:</i></p> <p>The document needs a stronger focus on sustainability and the carbon footprint. There is a section on waste disposal</p>	The comment is acknowledged but is outside the scope of this guideline (quality requirements rather than environmental sustainability). No change to the guideline is proposed.

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		<p>and plastics but it needs a subsection somewhere looking at the environmental impact of the device in terms of:</p> <ul style="list-style-type: none"> - Carbon footprint of the delivery system including any propellant - Carbon footprint of the inhaler itself - A requirement to include this data in the patient information sheet with advice on how to lower the footprint e.g. by recycling <p>Policy</p> <p>On 1st January 2019 the Kigali amendment to the Montreal Protocol came into effect, presented by the United Nations Environment Programme committing countries to phase down the use of F gases (see for asthma inhalers see ozone.unep.org).</p> <p>UK response as an example of a country with substantial improvement needed:</p> <p>In the UK Metered-dose inhalers make up 4% of the NHS' carbon footprint, and therefore the UK Parliament has initiated a programme to address this.</p> <p><i>"We recommend that low GWP inhalers should be promoted within the NHS unless there are specific medical reasons for not doing so. Promotion should include raising awareness of low GWP inhalers and training amongst NICE, the medical community and patients. The NHS should set a target that by 2022 at least 50% of prescribed inhalers are low GWP. It should publish annual progress reports. We were disappointed to find that so few MDIs are disposed of responsibly. We therefore recommend that the Government should work with medical professionals, pharmacists, the pharmaceutical industry and patients to significantly improve the recycling of MDIs; this makes both environmental and economic sense. The Government should ensure that by</i></p>	

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		<p><i>2020, at least 50% of MDIs are recycled. The Government should publish annual data showing progress in reaching and exceeding this target. It should also consider medical waste, such as MDIs, in its waste strategy."</i></p> <p>https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/46908.htm</p> <p>AIM OF THIS UK PROGRAM:</p> <ul style="list-style-type: none"> - Reducing carbon emissions of inhalers by 50% over the next 10 years - Reduce unnecessary prescribing of inhalers and shift to lower carbon options where clinically appropriate - Improve knowledge about inhaler use through training - Increase the recovery and recycling rates for used propellant canisters - Develop alternatives with less impact on climate change or better efficiency <p>WHY THIS PROGRAM IS IMPORTANT</p> <ul style="list-style-type: none"> - 70% of inhalers prescribed in the UK are metered-dose inhalers, which contain fluorinated gases (F-gases) as propellants, which are potent greenhouse gases - There are more than 65m inhalers prescribed every year, a very high proportion of which go to landfill with almost half of their usable propellant left inside - The impact of these propellants is equivalent to the carbon emissions from all NHS road mileage in England, including business travel and emergency vehicles <p>HOW GOALS NEED TO BE ACHIEVED</p> <p>The National Working Group on Reducing the Climate Change Impact of Inhalers is chaired by the SDU. They are collaborating and engaging with industry to build a comprehensive delivery plan for the coming years. This is</p>	

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		<p>work in progress as we put together the 19/20 plan. The plan is likely to include:</p> <ul style="list-style-type: none"> - Offering patients lower carbon options depending on clinical and medical suitability, for example dry powder inhalers; MDIs with lower volume of propellant, less puff per dose or visible dose meters - Supporting better prescribing practices, including more accurate diagnosis and reducing over-prescribing - Improving recovery and recycling levels of inhalers, including the canisters and propellant left over - Encouraging better training on inhaler use, with regular reviews - Collaborating with industry to develop propellants with less impact on climate change <p>There is now a Sustainability group of the NHS: https://www.sduhealth.org.uk/. And a particular group looking at inhalers: https://networks.sustainablehealthcare.org.uk/networks/sustainable-respiratory-care/expert-working-group-reducing-climate-change-impact-inhalers</p> <p><i>Suggestions for change:</i> Follow the UK sustainability example to diminish the impact of inhalers on the environment.</p>	
5	3	<p>Medicines for Europe welcomes the publication of this guideline as it represents an important milestone for the implementation of the Medical Device Regulation.</p>	<p>The comment is acknowledged.</p>

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6	5	<ul style="list-style-type: none"> Procedural aspect: Is it intended to consult this document within MDCG before publication (and will it be cross referenced in the MDCG guidance section)? Is it acceptable to prepare a NBOP before the MAH send the application to the competent authority, and therefore without referencing the marketing authorization procedure number? Will the NBOP made available to any 3rd parties? It is not clear how to handle the art 117 devices that were placed on the market before May 26, 2020 but never had a NBOP and now offer a change requiring NBOP. Does the NB need to assess all applicable GSPR to the device or only the ones affect by the change? 	<p>Discussions with the Commissions were held before finalising the guideline.</p> <p>Reference is made to the updated Q&A on the implementation of the Medical Device Regulation.</p>
7	6	<p>The guideline is rather extensive. Separate sections are applied to integral and non-integral DDCs including largely overlapping guidance on most aspects. It is recommended to combine guidance for integral and non-integral and specifically indicate where guidance is only applicable to either integral or non-integral DDCs in order to make the guideline more concise and avoid inconsistency between these categories.</p>	<p>The comment is acknowledged. The format of the guideline was considered prior to drafting and the current format is considered to be the clearest approach. The content of the guideline was revised following public consultation but the distinction between integral and non-integral devices is considered important due to different data requirements.</p>

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8	6	The proposed guideline focusses only on new DDC applications with referral to pivotal and/or bridging clinical studies. Is there any guidance foreseen for generic / hybrid DDC applications where comparability with an innovator DDC is also considered relevant? In addition, guidance on the comparison of the usability of such a generic/hybrid DDC vs the registered 'innovator' is requested.	The comment is acknowledged. Generic/hybrid applications are not excluded from the scope of the guideline. No specific reference is made since from a quality point of view the guidance provided is relevant.
9	6	The guideline does not address any aspects related to the added value of a DDC. Although usability is discussed in the guideline, it is recommended to also state how to assess if the new DDC is of added value to the user.	The comment is acknowledged however the value of a DDC will be included in the benefit/risk assessment for the DDC and will be a case-by-case assessment by the Competent Authority. EU legislation does not require that new medicines be superior to medicines already on the market. EMA evaluates medicines on the basis of their benefits and risks. Once a medicine is authorised, the decision to use it is taken by healthcare professionals who also take into account national guidelines as well as decisions of HTA bodies.
10	8	The guideline specifies regulatory requirements, which are considered in both regulatory frameworks (Medical Devices and Medicinal Products). This leads to a complex situation of different stakeholders, who have certain responsibilities within the different environments: Competent authorities (CA) for Medicinal Products and Medical Devices, Marketing Authorisation Holder (MAH), the Notified Bodies (NB) and the devices manufacturers. The technical assessment by a third party concerning Medical Devices is entrusted to the NB, while the device manufacturer stays responsible and liable for the product in most cases. Also, the new Medical Device Regulation (MDR) and this guideline leaves no doubt on this allocation of duties. However, due to the differences between those two frameworks we consider it is highly likely that divergent	The comment is acknowledged. Reference is made to the core precept of this guideline. The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit. The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.

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		<p>assessment strategies may be employed in the two regulatory frameworks (Medicinal Products & Medical Devices) at stake. Such fundamental differences in the assessment practice may lead to delays in the resolution of practical and technical problems. Consequently, it may affect the innovative power resulting in prolonged innovation times and increase of costs.</p> <p>For this reason, we are missing some details how such divergent opinions in the two legal frameworks may be avoided and what measures are taken by the CA to avoid or settle such systemic conflicts. In particular, the technical details requested by this guideline are frequently already assessed in detail by the manufacturer and the responsible NB. Therefore, unfavourable opinions on the performance parameters of the device need to be discussed again in the medical device framework (in most cases with the NB).</p> <p>For those reasons we would like to bring the following proposal to the attention of the agency: We consider that an option for joint meetings and clarifications, where all stakeholders are involved can reduce the risk for divergent regulatory approaches. Such activities might be done in form of:</p> <ol style="list-style-type: none"> 1) via Joint Scientific Advice Meetings (at pre-submission stage) <p>or</p> <ol style="list-style-type: none"> 2) we consider there should be an option for direct exchange between the CA and the NB, provided the MAH agrees and the MAH should be aware of the exchanged positions (during the evaluation phase of an application) 	

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11	9	<p>APPLICABILITY</p> <p>We welcome greater clarity on dossier requirements for Drug-Device Combinations (DDCs).</p> <p>However, as the implementation date for this draft guideline is not precisely defined, we suggest that any submission prior to or during implementation is not required to follow the final guideline. Only submissions after the referenced Regulation (EU) 2017/745 is fully applied on 26th May 2020 (assuming this draft guideline is also finalised prior to or on that date) would then be expected to follow the final guideline.</p>	<p>The Medical Device Regulation came into force on 26 May 2021. The guideline will come into force on 1 January 2022.</p>

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12	9	<p>CRITICAL – DEFINITIONS (1)</p> <p>The MDR 2017/745 mentions in “Whereas” (20) that the definitions regarding devices should be aligned with well-established practice in the field at EU and at international (e.g. US FDA definitions) level in order to enhance legal certainty. We would like to raise concerns regarding the use of the wording “medical device component” by the EMA to describe the device part of a DDC, whereas the US FDA defines a “medical device component” in 21CFR820.3(c) as meaning “<i>any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device</i>”, and whereas “crucial (medical device) components” and “critical suppliers of (medical device) components” are terminologies used under MDR 2017/745 with a meaning that is different from the EMA meaning (“device part of a DDC”). For the sake of having unambiguous definitions and enhance legal certainty in Europe, we suggest that the terminology “device constituent” be used by EMA instead of “device component”.</p>	<p>After consultation with the Commission, the term device (part) is considered the most appropriate terminology for the guideline.</p>

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13	9	<p>CRITICAL – DEFINITIONS (2)</p> <p>The EMA understanding of what the device part of a DDC covers is crucial to clarify: is it covering only the piece that is indeed administering the drug (e.g. the dropper), and not the container, or is it covering the total assembly of the container with the administering piece? The consequences from an EMA and NB reviews are substantial because it impacts on the split between what the NB and the EMA intend to review, and therefore on how the manufacturers intend to organize and split their data between their MAA and the documentation subject to NBOp (NBs are supposed to review the “device part”, and not the container).</p> <p>IPAC-RS recognizes that there is a difficulty defining “device part” and “drug part” in various scenarios, so we would encourage EMA to establish a dialogue among all stakeholders regarding definitions and invite public comments further, perhaps outside this particular guideline’s process, as a more general discussion.</p>	<p>The comment is acknowledged. The terminology in the final guideline reflects the outcome of the discussions with the Commission.</p> <p>Discussions were also held with Notified Bodies in the context of the development of the guideline.</p>
14	9	<p>DEFINITIONS (3)</p> <p>DEFINITION OF TERMS INCLUDING THE WORD “CLINICAL”</p> <p>The draft guideline uses the following terms in relation to the word <i>clinical</i>: investigation, trial, development, study, setting. It would be valuable to have agreement on these terms in the context of the DDC draft guideline. ...</p>	<p>The comment is acknowledged. The terminology in the final guideline and updated Q&A reflects the outcome of the discussions with the Commission.</p> <p>A definition on usability is included. The focus of the guideline is on quality requirements and definitions for the other terms mentioned in the comment were not considered necessary.</p>

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		<p>Clinical Trials – assess the safety and efficacy of the active drug(s) in the DDC (and can additionally be used to assess Usability aspects)</p> <p>Clinical Studies – assess the safety and efficacy of a medical device (and can additionally be used to assess Usability aspects) but are not relevant to DDCs (??)</p> <p>Usability (Human Factors) studies – assess the ability to use the medical device or DCC correctly and can be conducted in a clinical or non-clinical setting. DDCs should be used with placebo when in a non-clinical setting.</p> <p>Clinical Development / Clinical Investigation / Clinical Setting – these terms do not have defined meanings.</p>	
15	9	<p>CRITICAL – HARMONIZATION WITH OTHER STANDARDS</p> <ol style="list-style-type: none"> 1. The draft guideline mentions that “<i>Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.</i>” (line 171). However, flexibility should be introduced into the draft guideline relative to the use of harmonized standards published in the Official Journal of the European Union. Indeed, the presumption of compliance of the device or device-constituent part of a DDC to the applicable requirements of the MDR 2017/745 Annex I (GSPR) can be established based on the list of harmonized standards (Article 8). 	The comment is acknowledged. The text of the guideline was revised.

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		<ol style="list-style-type: none"> 2. Please include reference to other relevant guidelines, for example, Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, EMEA/CHMP/QWP/49313/2005 Corr as they also include guidance on what data to include on delivery device development. 3. Please also address the inconsistency with that existing guideline - Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" (EMA/CHMP/QWP/49313/2005 Corr (note this guidance was due to be revised in 2017, however this was put on hold). Anticipate that the inhalation and nasal guidance will be updated to align with this guidance and MDR. 4. Harmonize approach to (bio)compatibility by referencing ISO 10993 in lines 526-535. 	
16	9	<p>The draft guideline mentions in Annex 2 (Lines 812-815) a review process and NBOp for platform technologies referring to the CEP system (Certificate of Suitability to the monographs of the European Pharmacopoeia). IPAC-RS recognizes possible advantages of such a 'CEP-like' system (rather than a DMF-like system) meeting two key concerns raised by the Industry, which are focused around the potential streamlining of MAA/Variations management through one centrally evaluated and recognized uniform 'CEP-like' NBOp that could potentially support several MAAs. IPAC-RS understands through Lines 814-815 that this 'CEP-like' system could be used to provide evidence of compliance with the MDR Annex I GSPRs by one Notified Body for the same platform technology that is used across multiple drug-device combination</p>	<p>The comment is acknowledged but is outside the scope of this guideline. No change to the guideline is proposed.</p> <p>It is also noted that reference to CEP does not appear relevant since it refers to a different matter.</p> <p>After discussions with the Commission, the reference to platform technologies, for which there is no legal definition, was replaced with use of supportive data in the final guideline.</p>

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		<p>products. However, the implementation of this 'CEP-like' system needs to be clarified in the following respects:</p> <ul style="list-style-type: none"> - The legal basis and mechanism for this 'CEP-like' system needs to be clarified. It is not clear if this would be possible under the existing European legal & regulatory framework for medicinal products. - The definition of Platform Technology (PT) is not sufficiently clear and needs to be more precise. The term is commonly applied within the domain of drug product formulation technology, including manufacturing techniques and/or stabilizing ingredients for drug formulations. The platform may then be adapted to multiple active ingredients. For example to optimize aspects of physicochemical properties of certain drugs which lead to poor pharmacokinetics. Specific examples include patented technologies for microspheres, nanotechnology, liposomes, oral disintegration and sustained release formulations and manufacturing. Within the text of section 4.2 and the definition in section 10, the term PT may be applied to either formulation or device. Possibly this is the intent, however, this should be specifically stated in the definition (i.e. one (only) or both). - Within Annex 2 the responsibility for providing information on the PT is assigned to the 'technology owner' (Lines 812-813), with a table ("General Information") that is (in effect) "a letter of authorisation to the MAH to use the data". However, no mechanism for providing such data to an NB is 	

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		<p>defined. The LoA seems to be referring to a Drug or Device Master File type system which does not exist in Europe. Therefore how the 'letter of authorisation' process will work in practice should be clearly explained the CEP system as it is in place in Europe for pharmacopoeial substances does not use a "a letter of authorisation to the MAH to use the data". Rather, the CEP certificate itself is intended to be introduced in the MAA to replace the relevant data. Therefore IPAC-RS questions the need of a "letter of authorization" if a CEP-like process is implemented for PT.</p> <p>The CEP procedure for pharmacopoeial substances is optional. Currently in EU, there are 3 possibilities to submit pharmacopoeial substances data (CEP; Active Substance Master File (ASMF); Full data in the MAA). IPAC-RS recommends that the CEP-like system for a PT is also explicitly left optional by EMA.</p>	
17	10	<p>EUCOPE highly appreciates the publication of the EMA 'Guideline on the quality requirements for drug-device combinations' and welcomes the opportunity to comment. We have identified four general issues, the first one of highest impact, and some specific comments on the text.</p>	The comment is acknowledged.

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18	10	<p>Device documentation embedded in CTD module 3</p> <p>The guideline outlines that device documentation should be located in multiple sections of the eCTD Module 3 (P.1, P.2, P.3, P.5, P.7, P.8).</p> <p>EUCOPE strongly recommend to avoid any change of the (e)CTD structure and rather include the main elements of the device documentation in CTD 3.2.R. as a regional peculiarity for the EU, which would be in line in the eCTD overall concept.</p> <p>Our strong arguments are the following:</p> <ul style="list-style-type: none"> - Comply with the eCTD specifications published by the ICH M2 EWG and further developed by the ICH M8 EWG/IWG for eCTD v4.0, respectively - Avoid disharmonizing from ICH eCTD specification for the EU - Circumvent the need for technical adoption of eCTD DTD and eCTD specifications which would be a huge and unpredictable technical and operational burden - Fosters harmonization across regions as US FDA is already following this approach - Facilitate eCTD life cycle management to update the dossier post-approval 	<p>The comment is acknowledged and understood. The intention is not to deviate from eCTD but to ensure that information is appropriately referenced within the eCTD structure such that applicants will be aware of the data to support the device aspects and the assessor will be able to easily locate this information.</p> <p>Currently, information on integral devices in 3.2.R is often moved/duplicated in relevant 3.2.P sections if not included as a whole in 3.2.R. The objective is to have certainty over where the information is presented.</p>
19	10	<p>EUCOPE acknowledges the concept of a "letter of authorization" for a platform technology similar to the CEP for medicinal products and highly appreciates this pragmatic approach with regard to foster innovations. Further description of the concept would be appreciated, see specific comment line 190.</p>	<p>The comment is acknowledged and is addressed under specific comments.</p>

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			After discussions with the Commission, the reference to platform technologies, for which there is no legal definition, was replaced with use of supportive data in the final guideline.
20	10	<p>Clarify split of responsibilities / Table of content (ToC) for dossiers</p> <p>In order to clearly allocate information and avoid redundancy EUCOPE proposes an example of a split of the responsibilities by providing a ToC for the device documentation in relation to MAA dossier and NB dossier respectively, examples:</p> <ul style="list-style-type: none"> • Is Clinical Evaluation Report (CER) applicable for single integral DDC? • Should accuracy data for e.g. pre-filled injector or non-integral DDC both be submitted to CAs and NBs? • Is the DDC assembly part belonging to the NB review? • Should both CA and NB review the usability/human factor engineering report? • Summary risk assessment – should it also be evaluated by NB? <p>The intention is to avoid any duplicate assessment and maximize efficiency. Any exemption from this principle should be transparent preferably in the guideline (e.g. ToC example per MAA/NB dossier as an appendix).</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>

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21	10	<p>Co-pack product as part of the DDC definition</p> <p>The integration of documentation for co-packed DDC will make the option less attractive for the industry, although co-packed products are an important approach for future innovations and more convenient for patients. We suggest applying the same requirements as for DDC with labelling cross-reference.</p>	<p>The term "DDC" for which there is no legal definition, was removed from the guideline.</p> <p>Co-packaged medical devices are within the scope of this guideline. They are part of the medicinal product and data requirements may differ from those applicable to referenced devices.</p>
22	12	<p>EIGA members believe that medicinal gas packages incorporating a medical device such as a Valve with an Integrated Pressure Regulator (VIPR) or base units for liquid medicinal oxygen do not fall under this guideline and should be explicitly exempted.</p> <p>EIGA members also believe that the VIPR and base unit is not a non-integral DDC, because the device is part of the CCS, see line 81-82, 537.</p> <p>Detailed explanation:</p> <p>Line Nr. 64-66: This is not applicable to us because, the base unit and VIPR do not incorporate the substance itself and are only used to administer the drug.</p> <p>According to MDR Article 1(8) "However, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council (1), as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part are concerned."</p>	<p>As a general remark, medical device qualification and classification fall outside EMA remit.</p> <p>Including a specific reference to the example provided is not considered appropriate.</p>

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		Line Nr. 67-69: As the medicinal gas packages including the VIPR and the base unit are both reusable, medicinal gas packages, they do not fall under this requirement.	
23	13	<p>Case of Non-Integral Drug Device Combination: Diluent used in reconstitution kits:</p> <p>According to ICH M4, the Diluent shall have its dedicated 3.2 P section.</p> <p>In case of use of a Diluent already in prefilled syringes for the direct reconstitution of the Drug Product (and not for the administration for the patient), please clarify whether it falls under the article 1(8) of the MDR and will need to comply with article 117 and with the Annex 1 of the MDR.</p>	As a general remark, qualification of a product as a medical device, in this case a PFS intended for reconstitution only, falls outside EMA remit. However, a reference is made in the updated Q&A: "Some devices are not considered to form an integral product with the medicinal product and are treated as a container closure system e.g. nozzle on the top of the container for eye drops, syringe for reconstitution (without purpose for administration of the medicinal product) (...)".
24	14	The draft guideline is welcomed by industry and clarification in relation to the registration of drug-device combinations in the EU after May 2020 is appreciated. Especially, the terminology Integral and Non-integral is used in a consistent way. Co packed Medical Devices as Non-integral need to be CE marked.	The comment is acknowledged.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
25	14	<p>Comments in the general comments section are considered to be high priority. In addition, some specific comments are also regarded as high priority and are highlighted accordingly, in the specific comments section.</p> <p>The specific comments of high priority concern:</p> <ul style="list-style-type: none"> • Variation requirements for legacy products • Examples of integral DDCs where the device part is CE-marked • Clarification of the scope of the review of CA and NB to ensure complementary review and avoid duplication • Applicability of standards • Location of Usability and human factor studies in the CTD • Definition of platform technology • Labelling requirements for medical device component, and compliance with SmPC guideline • Inclusion in the package leaflet, of information related to the use of the DCC consistent with the device Instructions for Use. • Requirements for process validation • Risk-based approach for set up of control strategy • Level of requirements for stability program testing 	The comment is acknowledged.

26	14	<p>The approach suggested in the guideline raises serious concerns of duplication of review by the Competent Authorities (CA) and the Notified Body (NB).</p> <p>The guideline recommends to include very comprehensive device performance information in the quality module of the eCTD file which is in many cases also required as part of Annex 1 compliance.</p> <p>The overlapping information in Module 3 and the Notified Body (NB) submission will be assessed by both the Competent Authorities (CA) and the NB – this could be very burdensome, both for new submissions and during lifecycle management. During life cycle management there is a potential risk that updates of information could be missed as data is duplicated in multiple places.</p> <p>Since a summary report will be compiled by the NB, this will give an overview of the NB review of the device related aspects of the drug-device combination. It is therefore industry’s perspective that less information is needed in the CTD file itself. For example, the Guidance makes multiple requests for device related functionality testing throughout the proposed MAA submission structure. Comments have been added to individual lines below to reflect where there could be changes introduced to reduce duplication.</p> <p>In addition to this, Annex-1 (the proposed template for the NB opinion) is welcomed. Given that there will be an overlap of information presented in Module 3 of the dossier and the technical information assessed by the Notified Body providing the opinion, it would be beneficial to provide a high-level information on what are the general CA expectations on the overlapping areas (e.g. GSPR + functional performance). This will help the companies to ensure adequate communications with the NB to obtain timely NBOp.</p>	<p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
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Comment number	Stakeholder number	General comment	Outcome (if applicable)
27	14	<p>The draft guidance recommends that device content is distributed across the various existing 3.2.P sections of the MAA submission. It would be highly desirable to have the option of placing most of the device related information in a consolidated 3.2.R section with cross references as needed to the relevant 3.2.P sections. This is now a well-established industry practice and is in alignment with the FDA eCTD Technical Conformance Guide: https://www.fda.gov/media/93818/download</p> <p>This would avoid the inefficiency of MAA applicants being required to author separate Module 3 submissions to meet different dossier structure requirements from different regulatory agencies.</p> <p>This approach was also presented in the EBE reflection paper, published in January 2018: EBE reflection paper on "Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment"</p>	<p>The comment is acknowledged and understood. The intention is not to deviate from eCTD but to ensure that information is appropriately referenced within the eCTD structure such that applicants will be aware of the data to support the device aspects and the assessor will be able to find this information.</p> <p>Currently, information on integral devices in 3.2.R is often moved/duplicated in relevant 3.2.P sections if not included as a whole in 3.2.R. The objective is to have certainty over where the information is presented.</p>
28	14	<p><u>General comment for update of Notice to Applicant</u></p> <p>It is recommended that an update of the Notice to Applicant be planned in relation to this guideline as well as an update of the current variation guideline to reflect the requirements for the DDCs for lifecycle management.</p>	<p>The comment is noted. A revision to the Notice to applicants and classification guideline on variations, if considered necessary, would have to be agreed with the European Commission.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
29	14	<p>Bridging to an already market device seems to be proposed through MAA bridging. It is not clear if this can be utilised by a supplier of a device so that it can be used by multiple companies to access the same technology such as a pre-filled syringe. It is also not clear if a master file non-drug related NBOp or CE mark for a device component can be obtained and used for NB review. Moreover, it is not clear if a master file non-drug related NBOp or CE mark for a device component can be obtained and used with a letter of authorization and used if an additional NB review only on the additional drug specific aspects is needed and sufficient. Clarification and suggestions on how this could be managed will be welcomed.</p>	<p>The introduction of the concept of Device Master File is not currently foreseen in the EU legislation.</p> <p>Although a NBOp template was proposed as part of the draft guideline, the feasibility of a "core" NBOp + additional product-specific review falls outside EMA remit.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
30	14	<p><u>General comment for integral device</u></p> <p>Clarification of core precept (lines 155-7): The content of the Quality part of the dossier should focus on compatibility of the parts of the DDC in direct contact with the drug product, such as the primary packaging (in alignment with requirements for co-packed medical devices lines 532-3).</p> <p>Information on the secondary packaging with device functionality should be summarized to facilitate understanding of the working principle(s) and assurance of suitability/performance. The assessment of device part of the DDC functionality, safety and performance, is performed by the Notified Body and documented in the NBOp (in alignment with ambition to avoid duplication of assessment in line 441).</p> <p>It should be possible to adapt the information provided for the DDC in the MAA, provided that this is justified under a risk-based approach (in alignment with requirements for ATMPs lines 188-9).</p>	<p>A risk-based approach is applicable to integral devices.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application and reference is made to the core precept. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
31	14	<p><u>General comment for co-packed device</u></p> <p>Concern regarding the requirements for level of documentation in the MAA for the co-packed device (line 495-546).</p> <p>As the device is CE-marked, the level of information in the MAA should be risk-based. The co-packed device is CE-marked for the intended use, thus the information on the co-packed device included in the quality part should be high level to facilitate understanding of the working principle and suitability/performance.</p>	<p>The comment is acknowledged. A risk-based approach for co-packaged device is taken into consideration in the guideline.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
32	14	<p>Risks</p> <p>DDC risks should be integrated in the text, the risks should be evaluated from a DDC perspective and not only from a drug and device perspective.</p> <p>Risk based approach should be mentioned in General considerations.</p> <p>Risks should be mentioned under point 4.2 - Submission of data.</p> <p>Risks should also be mentioned in 5.2 - Module 3.2.P, Drug product where the product risks should be included, and the device risks should be summarised.</p> <p>5.4 - Module 3.2.R, regional Information, Medical Device should include a risk summary of the device.</p> <p>6.1.2 - Module 3.2.P, Drug product should include product risks and a summary of device risks. Only mentioned at row 584 referring to 3.2.P.2</p> <p>The use of risk-based approach for managing the life-cycle for DDCs and the submission of these changes is welcomed – Section 8 of guideline. Given that the EU variation classification guideline does not include detailed classification of variations and with the development of ICH Q12, it will be useful if the Agency provides additional information on the risk classification methodologies that could be applied for DDC related changes.</p>	The comment is acknowledged. The use of risk-based approaches is incorporated into the guideline.
33	14	What consideration is there in the guidance if a Medical Device as part of a DDC with NB certification (CE mark displayed) as a device, is suspended, withdrawn or revised?	This is a legal/procedural issue outside the scope of this scientific guideline.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
34	14	<p><u>Section 1: Introduction</u></p> <p>Definition of Drug-Device combination (DDC): It will be beneficial for the Agency to share a clear legal definition of the term Drug-Device Combination.</p> <p>Within the guideline, the term has been explicitly used and the scope is clearly defined. However, given the advancements of technologies and software, and no clear terminologies within the EU-Directives, it would be beneficial for new product developers to have a clear understanding of the legal terminologies.</p> <p>Throughout the document, different terms are used somewhat interchangeably, and not listed in the Definitions section.</p> <p>This may cause certain confusion or misinterpretation.</p> <p>Such terms are:</p> <ul style="list-style-type: none"> • Component • Components of the DDC • Constituent • Device component • Device part • Integral part • Integral DDC <p>Similarly, the expectations for information often refer to information on the DDC; or information related to the device. This should be checked throughout for consistency,</p>	The term DDC for which there is no legal definition was removed from the guideline.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		since these would often be different in practice. It is strongly recommended to expand the Definitions section.	
35	14	For some of the DDCs already on the markets that are to undergo a substantial design change to the device part, further clarity is required if all or which Module 3 documents/information as proposed in the guideline section 5 and 6 will have to be supplied as part of the variation dossier.	This matter has to be addressed on a case-by-case basis depending on the nature of the change and type of device. Therefore, it cannot be addressed as part of the guideline. Applicants are advised to liaise with EMA/Rapporteur/NCAs in case of doubt on the need to file a variation and appropriateness of the supportive data package.
36	14	Differentiation in terms of requirements should be made between innovating devices and standard (well known) devices.	Given the wide diversity of devices on the market and under development, this point cannot be addressed as part of the guideline. The concept of "standard" vs "innovative" may also evolve over time.
37	14	Add a cross-reference to the EMA-HMA-EC document "Electronic product information for human medicines in the EU – draft key principles". Electronic product information is an important future development and any new guideline that describes aspects of labelling should also consider these new developments.	References to QRD templates and SmPC guideline are included.
38	14	Questions and Answers of the EMA website should be considered more broadly in relation to the guideline. The key Q&A topics and information should be covered in this guidance itself in the relevant sections and not be addressed only in the separate Q&A. This includes sections from the Q&A on how art 117 will impact submission, timelines and updates to marketed products (1.3 Table 1; 1.5; 1.7).	An updated version of the Q&A agreed with the Commission was published in June 2021.
39	16	Suggest EMA to provide further guidance concerning the document package for notified body review against MDR Annex I.	Guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
40	17	Regeneron commends the Agency's work on this guideline on quality requirements for drug-device combinations. With the approaching implementation of the Medical Device Regulations (MDR), the guideline is an excellent early resource for introducing requirements within the MDR to Sponsors and other stakeholders.	The comment is acknowledged.
41	18	The MPP welcomes very much the publication of draft guideline and the opportunity to comment. The Guideline provides much needed and important clarity to Industry in many aspects related to complex combined devices or drug-device combinations (DDCs). Quality Management Systems (QMS) and manufacturers.	The comment is acknowledged.
42	18	<u>Quality Management Systems (QMS) and manufacturers</u> The Guideline is entitled "quality requirements for drug-device combinations," but it does not explicitly address the competent authorities (CA) expectations for QMS for the various components or supplier of device components. Can the Guideline confirm if components/devices manufactured by a Company holding an appropriate ISO 13485:2016 Certification would meet CA expectations for quality management systems?	The comment is acknowledged but the issue raised is considered out of scope of this guideline.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
43	18	<p><u>eCTD (Section 5 and 6)</u></p> <p>The guideline attempts to address the requirements covering the diverse spectrum of affected Stakeholders, which at times leads to repetition and therefore could be simplified e.g. Section 5 and 6.</p> <p>Further for section 5 and 6, a comparative table clearly indicating the required sections for the eCTD for the various possible options would improve clarity.</p>	<p>The comment is noted but the proposed table is not considered feasible or useful considering all possible scenarios depending on the type of medical device.</p>
44	18	<p><u>ATMPs and DDCs (Section 2)</u></p> <p>It is unclear if ATMPs are within or outside of the scope of this document.</p> <ul style="list-style-type: none"> - The document includes reference to ATMPs throughout (line 188[general reference], 413[container closure system], line578 [Non-integral DDCs]), even though it is stated that combined ATMPs (line 114-116) are excluded from the intended scope of the document. The inclusion of reference to situations where the device is considered a container closure system for the ATMP is not clear and is contradictory to the approach taken for other medicinal products. <p>Further clarity could be provided here by the inclusion of examples of such a closed container system for ATMPs.</p>	<p>The scope for ATMP takes into account the non-applicability of MDR Art 117 and the already existing guidance documents for this type of products.</p> <p>The text for ATMPs was updated in agreement with the Commission.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
45	18	<p><u>Guidance on MDR Article 22</u></p> <p>MDR Article 22 is not discussed in the Guidance, and its applicability in relation to DDCs is not clear</p> <p>If a Manufacturer co-packages a CE-marked device with their medicinal product, does Article 22 of the MDR on Systems and Procedure Packs become applicable to a marketing authorization holder (MAH)?</p> <p>Currently, the wording within paragraph (c) of Article 22 implies that medicinal products could be considered a “product” and can be co-packaged in such a system / procedure pack.</p> <p>Clarification within this document on the applicability of MDR Article 22 would be beneficial to clearly define the legal basis for co-packaged DDCs.</p>	In the guideline it is stated that system and procedure packs regulated under Article 22 of the MDR.
46	18	<p><u>Legal responsibilities of drug product and device manufacturers</u></p> <p>The legal basis and impact for Manufacturers is not clearly stated within the guidance.</p> <p>It is implied (line 674-676) that the drug product manufacturer is legally responsible for the DDC.</p> <p>Therefore, if a MAH of a medicinal product places a non-integral DDC on the market, do they take on the legal responsibility for the entire combination including the performance and safety of the device?</p> <p>Inclusion of a clear statement of liability and responsibilities would be beneficial.</p>	This point is considered out of scope of this guideline.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
47	18	<p><u>Notified Body Opinion Assessment</u></p> <p>The Notified Body Opinion is an important section which would benefit from being included as a stand-alone section of the Guideline.</p> <p>Of considerable value would be clearer guidance on specific core areas that the CA considers vital to be able make a Marketing Authorisation decision on the final integral DDC to minimise the risk of duplication of CA and NB assessments.</p> <p>The proposed Notified Body Template and cover sheet provides a useful basic information guide, which will, from a practical point of view, likely be incorporated into established internal processes and report templates currently used independently by Notified Bodies.</p>	<p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p> <p>A Notified Body Opinion template proposal was included in the draft guideline to stimulate discussions with Notified Bodies regarding expected information in the context of a marketing authorisation, line extension or variation application. However, such template is not within EMA/CHMP remit and it was decided to remove this proposal from the final guideline.</p>
48	18	<p><u>Notified Body Opinion Assessment of integral DDCs</u></p> <p>With the new requirement of a NB Opinion for new integral DDCs, it is important to industry that there is not a duplication of review between the CA and NB.</p> <p>It is unclear in the guideline if the assessment of an area performed by both the CA and NB, like usability data, shall review differing aspects and not have overlapping assessments.</p> <p>It would be beneficial if this was clarified in this Guidance.</p>	<p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
49	18	<p><u>Assessment of non-integral DDCs</u></p> <p>Further guidance would be beneficial on the CA expectations for assessment of co-packaged or non-integral DDC.</p> <p>Should a device be placed on the market as a standalone non-integral DDC, then while a CE Certificate may have been issued for the device component, the existence of this CE Certificate does not indicate that the NB has assessed the device's safety and performance for use in the final DDC.</p> <p>Additionally, for Class I devices that have no NB involvement but for which the CE-mark is applied by the device Manufacturer, this CE-mark does not guarantee that the use of the device in the suggested non-integral DDC configuration is in accordance with its CE-marked intended purpose.</p>	<p>Co-packaged devices are within the scope of this guideline.</p> <p>For example it is stated that evidence should be provided that relevant standards have been met e.g. EU Declaration of Conformity or, where applicable, EU certificate, or other appropriate documentation such as summary information confirming compliance with relevant GSPRs.</p>
50	19	<p>The prepared guidance is a much-needed addition to the regulatory landscape for drug-device combined products. The invested effort is recognised.</p>	<p>The comment is acknowledged.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
51	19	<p>As a consultant to both the pharma and the medical device industries; and with long-standing experience of developing, documenting, risk-assessing, submitting and maintaining drug-device combination products (Medicinal Products in this specific context), I remain a strong advocate of ensuring adequate focus on aspects related to the combination of the two constituents.</p> <p>Unfortunately, I see an absence of this in the draft guidance and foresee the Pharma industry using a potential 'gap' between Notified Body review and Competent Authority review to their advantage, whilst continuing to concentrate primarily upon the medicinal constituent rather than addressing the product as a system. From my perspective, this inherently poses patient risk and will likely lead to in-market discovery of quality, performance and use-related issues.</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
52	19	<p>With the scope as defined, the guidance needs to support both integral AND non-integral device constituents; and both Medicinal Products, and Medical Devices with ancillary substances. The level of generalisation versus specificity has been well-balanced to allow this, however it is clear that further supportive guidance will be needed.</p>	<p>This comment is acknowledged.</p> <p>This guideline is complemented for example by an EMA Q&A addressing procedural/regulatory matters.</p> <p>Ancillary substances are outside the scope of this guideline.</p>
53	19	<p><u>This review has focused on drug delivery devices (Art 1(9)) only.</u> Some of the comments below may prompt reflection on whether dedicated sections are required to address certain product types more specifically.</p>	<p>This comment is acknowledged. Responses are provided to specific comments.</p> <p>Reference to products defined by the second subparagraph of Article 1(8) of the MDR is included in the guideline.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
54	19	<p>Throughout the document, different terms are used somewhat interchangeably, and not listed in the Definitions section. This may cause certain confusion or misinterpretation. Such terms are:</p> <ul style="list-style-type: none"> • Component • Components of the DDC • Constituent • Device component • Medicinal component* • Device part • Integral part • Integral DDC <p>Similarly, the expectations for information often refer to information on the DDC; or information related to the device. This should be checked throughout for consistency, since these would often be different in practice. It is strongly recommended to expand the Definitions section.</p> <p>* the term medicinal component is used (line 77). I suggest this should be 'medicinal product constituent'.</p>	<p>The comment is acknowledged.</p> <p>The guideline has been revised with for example reference to device (part) and removal of the term DDC for which there is no legal definition.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
55	19	<p>When discussing non-integral DDCs, the text appears to be only describing the device constituent of such. Examples are often quoted as the device constituent only. The device constituent is not a non-integral DDC in itself – it must be associated with the Medicinal Product constituent. Non-integral DDCs incorporate both the device and the medicine in order to be a DDC. I suggest to review this aspect and ensure the term is used only when describing <u>both</u> the medicinal product <u>and</u> its non-integral device constituent.</p>	<p>The comment is acknowledged.</p> <p>The guideline has been revised with for example reference to device (part) and removal of the term DDC for which there is no legal definition.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
56	19	<p>The situation regarding currently authorised products is raising significant questions across industry.</p> <p>EMA Q&A 1.6 states in the context of impact on currently authorised products, that MDR Article 117:</p> <p><i>"...is not intended to apply retrospectively the requirements of the medical devices Regulation to medicinal products with an integral medical device already authorised or to those MAAs that have been submitted prior to 26 May 2020.</i></p> <p><i>However, if after authorisation there is a substantial change to the design or intended purpose of the device component, or a new device is introduced, any required certificate/declaration of conformity/NB opinion should be submitted as part of the variation/extension application, as appropriate to EMA/NCA."</i></p> <p>The statement <i>'However, if after authorisation...'</i> is not clear. Is it intending to state that MDR applies for a subsequent change to a <u>currently</u> authorised product; or simply a subsequent change to a product submitted on or after May 26th, 2020?</p>	<p>Art 117 of the MDR applies to regulatory submissions (MAAs, line extensions and variations) submitted as of 26/05/2021.</p> <p>Reference is made to the updated Q&A published in June 2021.</p>
57	19	<p>Section 1 defines several examples. It should be made clear that the 'designation' of these examples supersedes any conflicting information in current MEDDEV guidance.</p>	<p>The comment is acknowledged but is partly outside the scope of the guideline. The examples mentioned in the final guideline and updated Q&A (June 2021) were reviewed by the Commission).</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
58	19	<p>Section 5.1 requires the use of EDQM terminology.</p> <p>EMA should therefore consistently use EDQM terminology to support the quoted examples throughout the document, to avoid confusion.</p>	The comment is acknowledged.
59	19	<p>Structurally, the document has several repetitive sections. It may be of value to revisit and consolidate all discussion of certain topics into the same area. For example, Section 4.2/172-189 may be better positioned directly before section 5/205.</p> <p>It would appear that in addition to 'generic' information, there could be three major sections of the document, each addressing the specific requirements of the different configuration permutations, namely;</p> <ul style="list-style-type: none"> - Medicinal Product with integral administration device constituent - Medicinal Product with co-packed, CE-marked administration Medical Device - Medical Device incorporating Medicinal Product with the primary mode of action <p>Additionally, providing a summary matrix of requirements (as an Appendix?) may be very useful as a lookup either to the requirement or to the section where the requirement may be found.</p>	The comment is acknowledged. Reference is made to the final guideline which took into consideration all the comments received during public consultation.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
60	19	<p>Much of industry is assuming that the NBOp will take the place of further medicines Competent Authority review of the same data. It is likely that many pharma industry representatives raise issues regarding duplicated review as a result of this guidance.</p> <p>In my opinion, EMA should hold firm on this point.</p> <p>The Notified Body must review the device <u>and</u> the drug effects on that device; whilst the medicines Competent Authority must review the drug <u>and</u> the device impact on the drug. This will inevitably lead to certain duplicate review; albeit from different perspectives. Additionally, the NB has less legal accountability than when issuing certification to facilitate CE-marking of a Medical Device – in the NBOp process they are not granting market approval. The medicine Competent Authority is granting the overall approvability decision and must retain access to ALL data needed to enable this. One possible vehicle for this may be the NBOp report (depending upon how it is ultimately defined), however that should not automatically be assumed.</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
61	19	<p>It is understood by much of industry that the agency and inspectorate consider the combined product integration step of an integral DDC assembly, as functional secondary packaging. EMA should use this opportunity to clearly designate drug and device integration as an engineering assembly process and not a packaging process.</p>	<p>The point referred to is considered part of the drug product manufacturing process.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
62	19	The applicability of the MDR Art.117 text relies upon the core concept of the item being a device <u>if used separately</u> . Should we therefore be assessing the device constituent of an integral DDC 'separately' from the associated drug? This could make many things much clearer/simpler and would in fact align the NBOp mechanism more to a conformity assessment process.	The comment is acknowledged but a separate assessment of an integral device is not considered appropriate since many aspects are relevant for the quality, safety and efficacy of the medicinal product.
63	19	Finally, as a member or contributor to various discussion/working/industry groups it is possible that certain comments here are replicated in other 'submissions of comments' documents. This does not necessarily suggest that the comment is of any higher priority than any other.	The comment is noted.
64	20	<p>The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the</p> <p>entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.</p> <p>ACRO thanks the EMA for producing a helpful, detailed and comprehensive draft guideline on the quality requirements for drug-device combinations. In particular, ACRO welcomes the recognition of a risk-based approach to product</p>	The comment is acknowledged.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		development and data presentation so that alternative approaches for emerging technologies may be followed, if adequately justified. We also welcome and support the Agency's efforts to promote harmonisation of the format of Notified Body Opinions.	
65	23	<p>1) EMA and its regulatory role in marketing authorisations for drug-device combinations:</p> <ul style="list-style-type: none"> - Many medicinal products are combined with items that fall under the status of medical devices. These drug-device combinations play a major role in preventing medication errors. When poorly designed, poorly evaluated or poorly authorised, they can cause serious adverse effects and even death. EMA's obstinacy, for example, in authorising dangerous devices, such as both versions of the <i>fentanyl</i> iontophoretic transdermal system (Ionsys^o), or in not requiring that <i>levetiracetam</i> non-prefilled syringes (Keppra^o) be labelled with the patient age ranges for which they are intended, is worrying. - This public consultation relating to the new Medical Devices Regulation (EU/2017/745) is an opportunity for EMA to significantly strengthen its expertise in these health products and patient safety. EMA must safeguard its independence. Yet in its draft guideline it appears to be preparing the ground to become dependent on notified bodies (NBs) and medical device manufacturers. The recent scandals involving medical devices have shown the inability of NBs to guarantee the safety of patients who use these devices. Although Regulation EU/2017/745 appears in theory to strengthen the supervision and roles of NBs, they are likely to struggle to provide a service that increases the safety of health 	<p>The comments are generally considered outside the scope of this guideline.</p> <p>EMA and Notified Bodies have specific roles and responsibilities defined in the EU legislation. The authorisation and regulation of medical devices falls outside EMA remit. Reference is also made to the core precept of this guideline.</p> <p>The scope of the guideline was limited by the complexity of the evolving DDC landscape. However, updated or separate guidance can be considered as necessary.</p> <p>The guideline was developed in collaboration with EU Competent Authorities for the regulation of medicines and medical devices and the Commission was consulted. Discussion with Notified Bodies were also held</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>care if the number of NBs in the European Union falls. NBs only “verify” conformity with General Safety and Performance Requirements (GSPRs), while compliance with standards and guidelines is optional and conformity is simply presumed.</p> <ul style="list-style-type: none"> - Even if the new regulations on medical devices prove to afford a higher level of protection several years hence, the regulatory framework for medical devices, which follows the Global Approach, will never reach or approach that for medicinal products. The level of safety of medicinal products must not be dragged down by the weaknesses in regulations relating to medical devices. On the contrary, the regulatory framework for medicinal products should set the standard for the safety of medical devices. - We urge EMA to set up its own in-house specialised committee with expertise in medical devices, similar to the CAT or COMP committees on which the CHMP relies to reach marketing authorisation decisions. Civil society expects EMA and national drug regulatory agencies to engage effectively in the safety of patients who use medical devices, especially devices for use by or on individual patients. It seems inconceivable to us that responsibility for evaluating and authorising high-risk medical devices in the European Union will not return to health authorities sooner or later. EMA has a central and major part to play in preparing for this development. The EMA Committee for Medical Devices would liaise with the Medical Device Coordination Group (MDCG). - EMA has other aspects to address, such as organising the traceability of medical devices included in medicinal products, involving the unique device identifier (UDI) 	

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		<p>system that is due to be rolled out. How quickly and effectively will EMA respond to incidents involving such devices?</p> <ul style="list-style-type: none"> - Another issue is the matter of access to documents relating to the assessment of medical devices. The technical documentation for a medical device should be added to the marketing authorisation dossier and be accessible to any citizen through Regulation 1049/2001 on public access to administrative documents. In other words, drug regulatory agencies have a responsibility to centralise and disseminate information relating to the safety of the drug-device combinations they authorise. - It is up to EMA to ensure that these medical devices are subject to vigilance. Currently however, there is no European medical devices vigilance process apart from the "Task Forces", and Member States' participation in these is optional. EMA should lead efforts to establish a European vigilance network for medical devices. This would be a task for the Committee for Medical Devices. - EMA should encourage manufacturers to provide certificates confirming full compliance with European harmonised standards pertaining to the manufacture of the drug-device combinations it authorises. These certificates should be issued by independent third-party certification bodies (other than the NB involved in the CE marking process). This would be far safer than the voluntary full or partial application of standards, and self-certification of compliance with these standards by manufacturers. NBs do not verify compliance with standards with the same rigour as drug regulatory agencies verify medicinal product applications. Would EMA consider allowing marketing 	

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		<p>authorisation applicants to self-certify their medicinal products?</p> <ul style="list-style-type: none"> - As the EMA draft guideline points out, non-integral drug-device combinations (e.g. with a co-packaged medical device, such as a non-prefilled syringe provided for the oral administration of <i>levetiracetam</i> (Keppra®)), are very common and increasingly so, and integral drug-device combinations, such as the <i>fentanyl</i> iontophoretic system are likely to become more commonplace. It is likely that software and algorithms, in particular “artificial intelligence”, will also become more common in the coming years. What are EMA’s plans for covering the growing need for expertise in these areas? For example, how will EMA assess the first “smart” prefilled insulin pen? Will its EPAR include detailed information about the harm-benefit evaluation of the medical device part, i.e. the software and its algorithm? The obvious home for such expertise would be within EMA’s Committee for Medical Devices. We also have concerns about the quality of conformity assessments, user testing, and evaluations of the risk of errors and usability, given that there is no template showing the information that is expected and therefore no guarantee that the appropriate information will be provided. - The EMA Committee for Medical Devices would also need to monitor “drug look-alike” medical devices. There are increasing numbers of such poorly packaged products in the self-medication sector, especially from online retailers, which deceive consumers into thinking they are medicinal products. Who has the legitimacy to ban them if not drug regulatory authorities? For now, only national authorities have taken action against such products, albeit rarely, by referring them to the European 	

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		<p>Commission, one example being Commission Implementing Decision (EU) 2017/1445 that <i>cranberry</i>-containing products do not qualify for medical device status for which the opinion of the CHMP was requested.</p> <ul style="list-style-type: none"> - We urge EMA to make sure that the requirements for variation procedures are as stringent as those for initial marketing authorisation applications, especially as far as the prevention of medication errors is concerned. - Finally, we would like to ask whether this guideline was developed in conjunction with the HMA, i.e. all the national drug regulatory agencies. 	
66	23	<p>The purpose of most medical devices in drug-device combinations is to prepare and/or administer doses of the medicinal product. Our recommendations on such devices are as follows:</p> <ul style="list-style-type: none"> - Although this consultation concerns the quality part of the marketing authorisation dossier, EMA is right to propose firm links between quality modules and clinical evaluation modules in this area. In our view, separating expertise in quality from that in clinical safety and efficacy could endanger patients. - Favour unit-dose packaging, to prevent the risks associated with the use of dosing devices. - Refuse any marketing authorisation or variation application if the dosing device is not provided. It is insufficient to refer to a specific dosing device in the summary of product characteristics (SmPC) that patients should obtain separately from a health professional or company, or might buy on the internet. 	<p>The comments are noted but many aspects are considered outside the scope of this guideline.</p> <p>The use of separately-obtained medical devices referenced in the SmPC is considered acceptable when justified. Guidance is provided for such devices, following a risk-based approach in relation to the impact on the quality, safety and efficacy of the medicine.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<ul style="list-style-type: none"> - Oral liquid preparations must not be measured using household spoons or droppers. - Refuse on principle mass-produced (non-integral) dosing devices that are not labelled or embossed with information specific to the medicinal product they accompany. - Take other potential sources of danger into account: conversion from mg to mL; two different graduation scales on the same dosing device; potential confusion between dosing devices from the same range; etc. - Present EMA's evaluation of these risks clearly and in detail in EPARs. - EMA must systematically require marketing authorisation applicants to have user tests carried out by target patient groups or health professionals. This applies not only to injectable and oral liquid drugs, but also to oral solid forms with unusual, complex packaging (e.g. oral chemotherapy drugs). - These recommendations are mainly aimed at protecting children, elderly patients, and patients undergoing high-risk hospital care. When marketing authorisations are extended to include paediatric populations, we regularly find that the means to treat them have not been adequately addressed: suitable dose strengths have not been marketed and a dosing device for accurate preparation of small doses has not been included in the box. <p>We urge EMA to take account of national and international guidelines concerning the quality and safety of dosing devices.</p>	

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		We would also like to take this opportunity to ask EMA to add packaging mock-ups to EPARs, as it was recommended to do by the European Pharmacovigilance Risk Assessment Committee (PRAC).	
67	24	<p>It should be clarified that this guideline does not apply to packaging material as such nor to container closure systems used for medicinal products. Container closure systems for medicinal products do not fall within the scope of Article 1 (9) MDR because the definition of medical devices as laid down in article 2(1) does not apply to container closure systems without delivery function.</p> <p>Parts of the container closure that are currently additive components and not certified as a medical device would have to be certified as medical devices. Depending on the risk class the legal manufacturer has to involve a notified body to perform the conformity assessment procedure.</p> <p>We propose to exclude container closure systems from this guideline. It should remain "state-of-the-art" regulated through current regulations for medicinal products.</p>	Medical devices can act as container closure system when they contain and protect the dosage form. Therefore, they are in the scope of this guideline and guidance is provided for specific CTD sections.
68	24	<p>According to MDR Annex I 15.2.*) and Riemkus, Stieneker 2017**) only medical devices with an integrated container closure system including a measuring function with labelled S.I. units fall under this guideline (scope – integral DDC's).</p> <p>Other integrated container closure systems are part of 2.3.P.7 (CTD) of a Marketing Authorisation Dossier of a medicinal product.</p> <p>Used container closure systems, not certified as medical device, have to fulfill the requirements of chapter 3.2. –</p>	<p>The comment is noted.</p> <p>Medical devices do not need to have a measuring function to fall under the scope of the guideline.</p> <p>Guidance on container closure systems is provided under the dedicated CTD sections.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)						
		<p>containers- of Ph.Eur and the specifications of the current Ph.Eur. monograph of the respective medicinal product.</p> <p>*) 15.2 The measurements made by devices with a measuring function shall be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC.</p> <p>**) Rimkus et Stieneker.2013.Pharmazeutsche Packmittel.2.Auflage. S.320-336</p>							
69	24	<p>In general, it should be made clear (e.g. by providing examples) which (quality) aspects of the medical device part/DDC are assessed by the notified body and which aspects are assessed by the competent authorities; especially as duplicate assessment (see line 441) should be avoided; e. g.</p> <ul style="list-style-type: none"> • by providing advice which data should be stated in the MAA dossier and which in the technical documentation • by providing advice which documents of the technical documentation could be used as part of module 3 and where to locate them in the TD or Module 3 (e.g. as a comparative overview in an Annex) <table border="1" data-bbox="485 1187 1087 1284"> <thead> <tr> <th data-bbox="485 1187 753 1235">Type of document</th> <th data-bbox="753 1187 894 1235">TD</th> <th data-bbox="894 1187 1087 1235">Dossier</th> </tr> </thead> <tbody> <tr> <td data-bbox="485 1235 753 1284">....</td> <td data-bbox="753 1235 894 1284"></td> <td data-bbox="894 1235 1087 1284"></td> </tr> </tbody> </table>	Type of document	TD	Dossier			<p>The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
Type of document	TD	Dossier							
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Comment number	Stakeholder number	General comment	Outcome (if applicable)
70	24	<p>Unclear is the date from which this Guideline has to be applied on and if there will be a grace period.</p> <p>With regard to the MDR and the date it has to be applied on, this additional guideline with its scope can cause once more delays in assessments/ opinions from Notified bodies. It is noted that the procedure of getting NB opinion is out of scope of this guideline, however, it is still unclear how many Notified Bodies will be accredited and if there will be timeslots for requested services due to this Guideline. Due to the current situation in Europe and the fact that the Regulation (EU) 2017/745 on medical devices (MDR) has to be applied from May 2020 on the workload of the notified bodies is very high. It will hardly be possible to find a notified body for the CE-certification and perform the conformity assessment procedure in a timely manner.</p> <p>Furthermore this guideline means additional workload for the NCAs with regard to MAAs/variations.</p> <p>The timeframe for research & development of primary packaging/container closure systems plays a big role.</p> <p>New developments may cause further delays and at last a supply gap.</p>	<p>The guideline will come into force on 1 January 2022.</p> <p>Notified Body capacity is an issue outside EMA legal remit.</p>
71	24	<p><u>Transdermal patches:</u></p> <p>Generally, Transdermal drug delivery (TDD) is a non-invasive route of drug administration, using skin permeability to deliver the drug through the skin into the systemic circulation. No part of the patch system, e.g. adhesive, backing layer and release liners and rate control membrane (Ref. section 4.2.3 of EMA/CHMP/QWP/608924/2014), could clearly defined as</p>	<p>Qualification of a product as medical device falls outside EMA remit.</p> <p>Reference is made to the updated Q&A (June 2021) regarding the transdermal patch example.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>medical device part. Following this, transdermal patches falls under the scope of Article 1(2) of Directive 2001/83/EC.</p> <p>This is also confirmed in the guideline of modified release dosage forms (EMA/CHMP/EWP/280/96), Ph.Eur. Monograph 1011 "transdermal patches" and „Guideline on quality of transdermal patches" (EMA/CHMP/QWP/608924/2014), which has become effective in June 2015.</p> <p>In light with these and in order to avoid double regulation, we would like to seek clarification on what is regarded as device part in those patches for transdermal drug delivery which deliver the drug through the skin by passive diffusion (i.e. „passive patches" which do not make use of active delivery techniques like iontophoresis etc.).</p>	
72	25	<p>1. When going through the draft guideline it appears to endorse a double assessment in the sense that it proposes that the drug authority assess issues which have already been assessed by the Notified Body. And from a 'lex specialis'-analogue it can be argued that since the Notified Body will be equipped with device knowledge and competences the assessment of the device lies better with the Notified Body.</p> <p>2. Although the proposed guideline does require device change control, a risk management system and compliance with GSPR, the guideline is silent regarding requirements for a QMS that controls de medical device part of an integrated DDC. Although a NBOp does not require any assessments of the QMS for the device part of a DDC it is expected that applicants have ensured an adequate QMS has been established, implemented and maintained for the device part of an integral DDC. Such a QMS meets requirements of MDR Annex IX; in particular "design Control" must be applied.</p>	<p>1. The core precept of this guideline is that the CA responsible for the regulation of medicines will evaluate the device (part) specific aspects relevant to the quality safety and efficacy (and hence overall benefit/risk determination) of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs for the device (part).</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>3. In addition, draft guidance indicates a level of control for all changes to medical device and/or device components within DDCs that is not in anyone's interest – when considering continues improvements. This could lead to 'design freeze'.</p> <p><u>4. The guideline suggests that all device information must be submitted in the Module 3 P section. Some manufacturers provide this information in the Regional section. It is Medicoindustriens suggestion to keep all device-relevant information together and that it is optional whether the information is supplied under P or Regional-section.</u></p>	<p>2. The comment is noted but QMS for a medical device is considered outside the scope of this guideline.</p> <p>3. This matter has to be addressed on a case-by-case basis depending on the nature of the change and type of device. Therefore, it cannot be addressed as part of the guideline. Applicants are advised to liaise with EMA/Rapporteur/NCAs in case of doubt on the need to file a variation and appropriateness of the supportive data package. Reference is also made to specific comments.</p> <p>4. The comment is acknowledged and understood. The intention is not to deviate from eCTD but to ensure that information is appropriately referenced within the eCTD structure such that applicants will be aware of the data to support the device aspects and the assessor will be able to find this information.</p> <p>Currently, information on integral devices in 3.2.R is often moved/duplicated in relevant 3.2.P sections if not included as a whole in 3.2.R. The objective is to have certainty over where the information is presented.</p>
73	26	<p>The draft guideline on the quality requirements for drug-device combinations describes the quality requirement for a combination product. Our understanding is that this guideline includes patches whatever the type, transdermal and non-transdermal (transdermal devices are mentioned line 269 but not defined in the examples of section 1). If confirmed, we would suggest to include a reference to patches in the section 1 Introduction (background) as integral DDCs.</p> <p>A Guideline on quality of transdermal patches (EMA/CHMP/QWP/608924/2014) describes the quality requirement for a transdermal or a cutaneous patch. The present guideline on drug-device combinations should be</p>	<p>Qualification of a product as medical device falls outside EMA legal remit.</p> <p>Reference is made to the updated Q&A (June 2021) regarding the transdermal patch example.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>consistent with the guideline on quality of transdermal patches. We have noted some discrepancies in location requirements of information related to device and device components when the device is a patch. Please refer below in section 2 specific comments on text for details. We would suggest to align both guidelines and /or well define the scope of the present guideline compared to the guideline on transdermal patches.</p>	
74	27	<p>EFA welcomes the EMA initiative to the streamlining of quality requirements for DDCs, a type of products that has seen a rise in the number of applications for commercialisation, and are therefore becoming more and more used.</p> <p>DDCs are of great importance for the patient community EFA represents, given that allergy, asthma and COPD are chronic non-communicable diseases that need long-term medication. Treatments for allergy and airways diseases require adherence to be effective, which is linked to the regularity and correct dosing of the medicine intake. Therefore, EFA appreciates the increasing availability of DDCs, as their automated features fit well with the long-term needs of allergy, asthma and COPD disease management. As the paper correctly points out, DDCs have the potential to relieve patients from part of the disease burden. Besides this, certain DDCs are also vital in life-threatening situations e.g. adrenaline auto-injectors in the case of anaphylactic reaction.</p> <p>Finally, the alignment of quality requirements has the potential to stimulate further research into better and more efficient DDCs for the benefit of patients.</p>	The comment is acknowledged.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
75	28	<ol style="list-style-type: none"> 1. Is it appropriate that this <u>guidance</u> document defines a new term "Drug-Device combination product" (DDC) which is not founded in the EU pharmaceutical law – neither MDR nor 2001/83/EC? Would be more appropriate if the guidance was limited to cover article 117 related devices and NBOP's 2. Although the proposed guideline requires device change control, a risk management system and compliance with GSPR, the guideline should not be silent regarding requirements for a QMS that controls the medical device part of an integrated DDC. The NBOP does not require any assessments of the QMS for the device part of a DDC. It is expected that applicants have ensured that an adequate QMS has been established, implemented and maintained for the device part of an integral DDC. Such a QMS meets requirements of MDR Annex IX; in particular "design Control" must be applied. Propose to add guidance regarding the applied QMS. 3. In addition, draft guidance indicates a level of control for all changes to medical device and/or device components within DDCs that is not in anyone's interest – when considering continues improvements. This could lead to 'design freeze'. Guidance is needed on change control. See also comments to line 231, line 356, line 362, lines 363-366, lines 445-459, lines 481-482, line 556, line 610 and lines 628-642 	<ol style="list-style-type: none"> 1. The comment is acknowledged and the term DDC was removed from the final guideline. Limiting the scope of the guideline to Art 117 is not agreed. Guidance is considered necessary for non-integral medical devices. 2. This is considered out of scope of this guideline. 3. This matter has to be addressed on a case-by-case basis depending on the nature of the change and type of device. Therefore, it cannot be addressed as part of the guideline. Applicants are advised to liaise with EMA/Rapporteur/NCAs in case of doubt on the need to file a variation and appropriateness of the supportive data package. Reference is also made to specific comments.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
76	29	The guideline is still in draft. Is it already mandatory to implement the information in the medicinal product dossier and labelling at this stage? Is a transition period being considered, also in view of the MDR only being fully effective by May 2020?	The final guideline will come into force on 1 January 2022.
77	29	For non-integral DDCs (provided separately), the use of a device is optional. For example, pre-filled syringes might be used with a reusable auto-injector. But for some patients a manual injection might still be preferred. Is it considered necessary for this category of devices to include additional information, other than cross-referencing the IFU of that auto-injector and vice versa (the IFU referencing the medicinal product it can be used with)?	The comment is unclear. Reference is made to the section of the guideline on medicinal products with referenced devices. Reference is also made to the QRD templates and SmPC guideline regarding the information expected to support the use of the device.
78	29	According to the draft guidance, additional information regarding the use of a device (both integral and non-integral DDCs) needs to be included in the SmPC and PIL of the medicinal product. This is going to impact the readability of the SmPC and PIL. Will this require new user testing of the PIL?	The parts of the guideline related to product information have been revised with general principles references to the QRD templates and SmPC guideline.
79	30	<p>Pharmathen welcomes the guideline on the 'quality requirements for drug-device combinations' from EMA. This guideline will be very useful to understand the agency's new requirements on the drug-device combination products.</p> <p>The guideline states in the introduction (lines 54-55) that "a medical device/medical device component (hereafter, both terms are called 'device(s)', for definitions see Section 10)". The use of this term 'device(s)' is not observed at some places in the guideline which might lead to uncertainty.</p> <p>Specific comments regarding this general comment are provided in section 2.</p>	Reference is made to the responses to individual comments.

Comment number	Stakeholder number	General comment	Outcome (if applicable)
80	31	<p>General comment for integral device:</p> <p>Clarification of core precept (lines 155-157): The content of the Quality part of the dossier should focus on compatibility of the parts of the Drug Device Combination (DDC) in direct contact with the drug product, such as the primary packaging (in alignment with requirements for co-packed medical devices lines 532-533).</p> <p>Information on the secondary packaging with device functionality should be summarized to facilitate understanding of the working principle(s) and assurance of suitability/performance. The assessment of device functionality, safety and performance, is performed by the notified body and documented in the NBOp (in alignment with ambition to avoid duplication of assessment in line 441).</p> <p>It should be possible to adapt the information provided for the DDC in the MAA, provided that this is justified under a risk-based approach (in alignment with requirements for ATMPs lines 188-9).</p>	<p>A risk-based approach is applicable to integral devices.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application and reference is made to the core precept. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
81	31	<p>General comment for co-packed device:</p> <p>Comment regarding requirements for level of documentation in the MAA for the co-packed device (line 495-546). As the device is CE-marked – the level of information in the MAA should be risk-based. The co-packed device is CE-marked for the intended use, thus the information on the co-packed device included in the quality part should be high level to facilitate understanding of the working principle and suitability/performance.</p>	<p>The comment is acknowledged. A risk-based approach for co-packaged devices is taken into consideration in the guideline.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
82	31	<p>Comment:</p> <p>It seems that a lot of the device information we have been providing in 3.2.R will now be spread out across 3.2.P.</p> <p>Proposed change:</p> <p>Would be more concise and aid in lifecycle management if device information can stay concentrated in 3.2.R.</p>	<p>The comment is acknowledged and understood. The intention is not to deviate from eCTD but to ensure that information is appropriately referenced within the eCTD structure such that applicants will be aware of the data to support the device aspects and the assessor will be able to find this information.</p> <p>Currently, information on integral devices in 3.2.R is often moved/duplicated in relevant 3.2.P sections if not included as a whole in 3.2.R. The objective is to have certainty over where the information is presented.</p>
83	31	<p>Please clarify the following aspects:</p> <ul style="list-style-type: none"> • Will combination products with design control-exempt devices require design controls? • Products already on the market: will they be grandfathered, or will there be a transition period to get into compliance? • What regulations apply to products that are out of scope per Lines 118/119? 	<p>The points raised are out of scope of the guideline.</p>
84	32	<p>Find in general this guideline very well written and important to clarify quality requirements for drug-device combinations.</p>	<p>The comment is acknowledged.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
85	33	<p>The draft guideline is welcomed by the Combination Products Coalition (CPC) and clarification in relation to the registration of drug-device combination products in the EU after May 2020 is appreciated. The CPC is pleased and encouraged to see the effort that is being made to address these important and complex issues.</p> <p>The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with regulatory agencies on issues affecting combination products to advance our common mission: providing the best possible health care to patients.</p> <p>http://combinationproducts.com/</p>	The comment is noted.
86	33	<p>The CPC has worked in partnership with the European Federation of Pharmaceutical Industries and Associations (EFPIA) to ensure consistent industry feedback on this important draft guideline. Therefore, the CPC is not submitting separate detailed comments under its own name. The CPC, however, fully endorses and supports the comments submitted by EFPIA.</p>	The comment is noted.
87	34	<p>AESGP welcomes the opportunity to provide comments on the guideline on quality requirements for drug-device combinations. AESGP appreciates the efforts to clearly define the quality requirements of an integral device and a non-integral device which is what this guideline focuses on.</p> <p>AESGP appreciates that medical devices' technology is progressing at a rapid pace and understands that for this guideline to remain relevant and adapt to emerging</p>	<p>The comment is acknowledged.</p> <p>Informal discussions with Notified Bodies were held during the development of the guideline.</p> <p>A Notified Body Opinion template proposal was included in the draft guideline to stimulate discussions with Notified Bodies regarding expected information in the context of a marketing authorisation, line extension or variation application. However,</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>technologies, updates to this guideline will be made in the future.</p> <p>Annex 1 proposes the new template for submission of Notified Body opinion. It may be useful to gain insight from Notified Bodies concerning this proposal. As this proposed template will result in additional work for the Notified Bodies, we request that Notified Body endorsement of this template is sought.</p>	<p>such template is not within EMA/CHMP remit and it was decided to remove this proposal from the final guideline.</p>
88	34	<p>1. Duplication of review.</p> <p>The suggested approach raises serious concerns of duplication of review. The guideline recommends the inclusion of very comprehensive device performance information in the quality module of the CTD which in many cases is also required as part of Annex 1 compliance. Overlapping documentation will be assessed by both the Competent Authorities and the Notified Body. There is a potential risk that updates of information to the device component, could be missed as data is duplicated in multiple places. The summary report compiled by the Notified Body will give an overview of the device related aspects of the drug-device combination. It is therefore industry's perspective that less information is needed in the CTD file itself. An overview on the CA expectations on the overlapping areas such as GSPR + functional performance would be helpful.</p> <p>2. Location of the quality information for the medical device in the CTD.</p> <p>The draft guidance recommends that device content is distributed across the various existing 3.2.P sections of the CTD. It would be highly desirable to have the option of placing most of the device related information in a</p>	<p>1. The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p> <p>2. The comment is acknowledged and understood. The intention is not to deviate from eCTD but to ensure that information is appropriately referenced within the eCTD structure such that applicants will be aware of the data to support the device aspects and the assessor will be able to find this information.</p> <p>Currently, information on integral devices in 3.2.R is often moved/duplicated in relevant 3.2.P sections if not included as a whole in 3.2.R. The objective is to have certainty over where the information is presented.</p>

Comment number	Stakeholder number	General comment	Outcome (if applicable)
		<p>consolidated 3.2.R section, which is currently a well-established industry practice and is in alignment with the FDA eCTD Technical Conformance Guide: https://www.fda.gov/media/93818/download.</p> <p>3. Master file for the device component</p> <p>Bridging to an already market device seems to be proposed through MAA bridging. It is not clear if this can be utilised by a supplier of a device so that it can be used by multiple companies to access the same technology such as a pre-filled syringe. It is also not clear if a master file non-drug related NBOP or CE mark for a device component can be obtained and used for NB review. Moreover, it is not clear if a master file non-drug related NBOP or CE mark for a device component can be obtained and used with a letter of authorization and used if an additional NB review only on the additional drug specific aspects is needed and sufficient. Clarification and suggestions on how this could be managed will be welcomed.</p>	<p>3. The concept of device master file is not currently foreseen in the EU legislation.</p>
89	36	<p>For DDCs which are non-integral and not co-packed with the medicinal product, it would be beneficial for the industry to provide guidance on the extent of information to be included in the SmPC/package leaflet (such as use of trade name of devices etc.) or would it be sufficient to just make the cross-reference to the IFU of the device?</p>	<p>Reference is made in the guideline to the EMA QRD template and SmPC guideline. It is also explained that "<i>The SmPC, labelling and package leaflet should not include details of the device manufacturer/authorised representative, CE mark (incl. NB number), device symbols, UDI or references to device market surveillance reporting</i>".</p>

2. Specific comments on text

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
GUIDELINE TITLE (L5-6)				
90	L5-6	18	<p>Comment: The Guideline purpose as defined in the executive summary is to provide guidance on the documentation expected for DDCs in the quality module of the CTD, however the title suggests a wider scope of the Guideline.</p> <p>Proposed change (if any):</p> <p><i>Guideline on the documentation requirements for the device component in for drug-device combinations</i></p>	The title of the guideline has been revised and reference to DDC, for which there is no legal definition, has been removed. The title covers the 3 categories of devices within the scope of this guideline.
EXECUTIVE SUMMARY (L42-50)				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
91	L43 and L101	5	<p>The purpose of the guideline is outlined as follows “This guideline provides guidance on the documentation expected for Drug-Device Combinations (DDCs) 43 in the quality part of the dossier for a marketing authorisation application or a variation application.”</p> <p>Guidance of the documentation does not include guidance on the assessment – in specific guidance on the assessment of the Notified Body opinion (NBOp) (e.g. investigation depth).</p> <p>Is it the section 3.2.R (demonstration of compliance of the device with MDR annex 1 GSPR) only?</p> <p>Both sections 3.2.P & R (cross-references to studies or information could have to be verified...)?</p> <p>Does EMA create a separate document on this topic?</p> <p>If EMA considers no guidance on the assessment of the NBOp, does EMA consider this to be in the individual responsibility of the respective Notified Body?</p> <p>Proposed change (if any):</p> <p>Provide clarity on the purpose of the guideline as well as its limitations.</p>	<p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review and gaps in review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
92	L43	21	<p>The used standard term is “Drug-Device Combinations (DDCs)”</p> <p>By FDA the standard term is “Combination product” - https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types . It is requested if is it possible to evaluate an harmonization of this standard term and others, to be used for the CTD.</p>	The comment is acknowledged. The term DDC was removed from the final guideline, including the title.
93	L44	14, 31	<p><u>HIGH PRIORITY</u></p> <p><u>Comment:</u> Unclear if this guidance applies to variations concerning legacy products (the scope of this guidance is initial MAAs and their subsequent variations per lines 108-9).</p> <p><u>Proposed change (if any):</u> For legacy products, we propose to add the following clarification:</p> <p>“For significant changes to the device constituent part of legacy products, it is sufficient to obtain an NBOp unless the change in the device constituent part affects the quality, safety and efficacy of the medicinal product. In this case, it would also require an update of the impacted Module 3 chapters.”</p>	<p>The guideline does not apply retrospectively</p> <p>The NBOp, when required, applies to applications <u>submitted</u> to EMA since 26/05/2021.</p> <p>EMA can advise on the need to submit a variation for a particular change. But advising on the substantiality of a change in relation to the need to obtain a new or revised NBOp is outside EMA remit. In case it is required for a post-authorisation application, the corresponding documentation is expected in the application submitted to EMA.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
94	L44	19	<p>Comment: <i>"This guideline provides guidance on the documentation expected for Drug-Device Combinations (DDCs) in the quality part of the dossier for a marketing authorisation application or a variation application."</i></p> <p>The documentation expected would depend upon the degree of change to the device constituent and the type of variation. Therefore, the guidance does not apply to <u>any</u> variation application.</p> <p>Proposed change: change text to '<i>... or certain variation applications.</i>'</p>	<p>The comment is acknowledged. A change to the device (part) may not necessarily result in a variation and/or a new or revised NBOp, or it may also require both. It has to be considered on a case-by-case basis.</p> <p>EMA can advise on the need to submit a variation for a particular change. But advising on the significance or substantiality of a change in relation to the need to obtain a new or revised NBOp is outside EMA remit. In case it is required for a post-authorisation application, the corresponding documentation is expected in the application submitted to EMA.</p>
95	L44	19	<p>Comment: EMA Q&A uses 'variation/extension' whilst this guideline uses 'variation'.</p> <p>Proposed change: Use consistent phrasing.</p>	<p>The final guideline refers to variation but principles also apply to extension applications to a marketing authorisation.</p>
96	L44	35	<p>With reference to the documentation expected for a variation application for a drug-device combination, the document "Questions & answers on implementation of medical devices and in vitro diagnostic medical devices regulations ((EU) 2017/745 and (EU) 2017/746" – EMA/37991/2019" details how to approach a change and the submission of a variation procedure for an integral drug-device combination according to MDR Article 117. It is not clear if the same approach and recommendations are also applicable in the case of a variation for a non-integral combination. Clarify how to</p>	<p>Reference is made to the updated Q&A (June 2021) and lifecycle management section of the final guideline (applicable to all 3 categories of devices).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			approach a variation procedure for a non-integral drug-device combination	
97	L44-47	14	<p>Comment: Incorrect differentiation of medical devices and medical device components in the context of DDCs.</p> <p>In the context of an integral DDC, the medical device part could be considered a component. In the context of a non-integral DDC (e.g. co-packaged), the device would be CE-marked and is therefore not a device component but a "stand alone" medical device.</p> <p>Proposed change (if any): For the purpose of this guideline, medicinal products which contain one or more medical devices(s) and/or medical device component(s) as an integral part of the composition, as well as medicinal products for which one or more medical device(s) are necessary for use of the medicinal product are defined as DDCs.</p>	The term DDC was removed from the guideline and reference is made to "device (part)".
98	L45-50	14	<p>Comment: Edit for clarity – the current wording is not so clear that we are talking about non-integral devices that are specific for use with the product. Propose condensing sentence to be clear.</p> <p>Proposed change (if any): For the purpose of this guideline, medicinal products which contain one or more medical devices(s) as an integral part of the composition, as well as medicinal products for which one or more non-integral, specific medical device(s) and/or device component(s) are necessary for use of the medicinal product, are defined as DDCs. The types of DDCs within the scope of this guideline are medical device(s) and/or device component(s) that are integral to the medicinal product or</p>	The comment is noted. The text was revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			non-integral (i.e. those devices that are co-packaged with the medicinal product or referenced in the medicinal product information and obtained separately).	
99	L45-48	3	<p>Comment:</p> <p>Devices that may be necessary for the use but are not specifically proposed by the applicant are not in scope of this guideline and should not be considered as DDCs. These could be syringes, infusion bags, or aids (e.g. swabs). It is therefore proposed to change “necessary” to “proposed”, with the meaning of “proposed by the applicant in the application dossier”.</p> <p>Proposed change (if any): “...as well as medicinal products for which one or more medical device(s) and/or device component(s) are necessary proposed for use of the medicinal product are defined as DDCs.”</p>	<p>The comment is agreed.</p> <p>In the section on medicinal products with referenced devices, it is explained that “<i>Where a medical device is referenced in the product information of the medicinal product and may have a potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product, additional information may be required. The requirements in this section do not apply where reference is made to a general group of devices (e.g. “using a syringe” or “an infusion line”, etc.)</i>”.</p>
100	L46-50	7	<p>Proposed change (if any): The types of DDCs within the scope of this guideline are medical device(s) and/or device component(s) that are integral to the medicinal product or non-integral (i.e. co-packaged with the medicinal product or referenced in the medicinal product information and obtained separately but physically combined for use).</p>	<p>The comment and proposed change is unclear.</p> <p>These 3 categories are within the scope of the guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
101	L49	14	<p>Comment: The scope of the guidance shall be more aligned to the Art 117 of the MDR. The scope of this guidance is too broad as it does not clearly state that it applies to devices components "if used separately".</p> <p>Proposed change (if any): Add "if used separately" after "device component(s)".</p>	<p>The comment is unclear.</p> <p>Limiting the scope of the guideline of the guideline to devices falling within the scope of Article 117 is not considered appropriate. Co-packaged devices and separately-obtained devices mentioned in the product information are also covered.</p>
102	L49-50	9	<p>Proposed Changed Text</p> <p><i>(i.e. co-packaged with the medicinal product or referenced through brand name/registration number/CE mark in the medicinal product information and obtained separately. Reference to generic types or classes of devices do not fall within the scopes of this guideline – i.e. administer using a suitable syringe/catheter etc.)</i></p>	<p>Co-packaged devices and separately-obtained devices mentioned in the product information are also covered. For the latter, it is explained in the guideline that "Where a medical device is referenced in the product information of the medicinal product and may have a potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product, additional information may be required. The requirements in this section do not apply where reference is made to a general group of devices (e.g. "using a syringe" or "an infusion line", etc.)".</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
103	L50	14	<p>Comment: Devices that are referenced in the medicinal product information may vary substantially. For example, an injectable product may be administered by using various type of IV infusion sets. Although the text of the guideline includes such scenarios, it will be beneficial that the Executive summary of the guidance includes a brief clarification.</p> <p>Proposed change (if any): [...] medicinal product or referenced in the medicinal product information (where SmPC includes use of specific device e.g. spacer) and obtained separately [...]).,</p>	<p>The comment is acknowledged.</p> <p>It is explained in the guideline that “<i>Where a medical device is referenced in the product information of the medicinal product and may have a potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product, additional information may be required. The requirements in this section do not apply where reference is made to a general group of devices (e.g. “using a syringe” or “an infusion line”, etc.)</i>”.</p>
104	L50	31	<p>Comment:</p> <p>Types of DDCs in scope of this guideline include medical device(s) and/or device component(s) that are non-integral, defined as “co-packaged with the medicinal product or referenced in the medicinal product information and obtained separately”. This one-way labelling is not consistent with how cross-labelled combination products are considered in the United States (i.e. mutually conforming labelling of the medicinal product and device).</p> <p>Proposed change/recommendation:</p> <p>To harmonize combination product definitions between the US and the EU and to aid in lifecycle management of dossiers, recommend altering the language to reflect mutually conforming labelling between the medicinal product and medical device.</p>	<p>The comment is acknowledged. Harmonising definitions with other regions is not within the scope of this guideline.</p> <p>It should be noted that the term DDC, for which there is no legal definition, was removed from the guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>1. INTRODUCTION (L51-97)</u>				
105	L45-97 L406-412 L502-507 L670-673 L684	4	<p>It is still not clear if the integrated or non-integrated dosing equipment has to be a medical device. The guideline uses the term medical device and device as synonyms (line 684).</p> <p>A clear distinction between the general term "device" and the specific term "medical device" as a special form of a device should be made, sustaining the option of a "device" being used as dosing equipment. Line 670-673 and line 684 should be adapted.</p> <p>It should remain the applicant's responsibility to decide whether the integrated or non-integrated dosing equipment is confirmed by means of a medical device certificate or by a quality based, sound reasoning presented as part of the container closure section.</p> <p>The latter approach is highly recommended for low risk products (mostly but not limited to OTC) for integral DDCs such as "devices for delivery to site of action (dropper or spray for throat spray" (line 71-72) and for non-integral DDCs such as "oral administration devises" (line 91) and "pumps for medical product deliveries" (line 96).</p> <p>This suggestion corresponds to lines # 406 – 412 as well as # 502 – 507, where the requirements to demonstrate the suitability / usability / safety / performance of the dosing equipment when used with the medicinal product are laid down.</p> <p>Please clarify.</p>	<p>The final guideline refers to "device (part)" and a definition is provided.</p> <p>The requirement for CE certification of medical devices is underpinned by legislation and cannot be changed.</p> <p>Low risk Class I integral devices do not require a NBOp unless of class Is/Im/Irs (where, if used separately, a NB would be involved in certification).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
106	L52-59	19	<p>Comment: It is not quite clear why such a guideline requires this very high-level text. It does not add guidance or clarify the positioning/scope.</p> <p>DDCs are used in broad applications, not exclusively to outpatients. The use of 'professional' is unclear – does this standalone as a term or only apply to 'caregiver'?</p> <p>Proposed change: Remove text</p>	The comment is acknowledged. The text has been revised.
107	L54 and L687	5	<p>Why is the term medical device component introduced?</p> <p>Proposed change (if any):</p> <p>Delete the term and the following explanation in parenthesis. 687: Move explanation into 684</p>	The final guideline refers to "device (part)".
108	L54 and L81	14, 19	<p>Comment: The difference between a 'medical device' and a 'medical device component' should be elaborated. Typically, 'component' is used in engineering terms to describe a single part that makes up a larger item e.g. screw, spring, button, moulded part, etc. In such a case, an 'integral component' does not automatically suggest an 'integral device'.</p> <p>However, line 81 uses the term 'component' more in the context of a constituent (i.e. the device part of a drug-device combination) whilst lines 213, 265 use the term in a manner more akin to a single engineering component.</p> <p>Proposed change (if any): Review all terms and check consistency.</p>	The final guideline refers to "device (part)".

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
109	L57	14	<p>Comment: These “devices” may be used in either an in-patient or outpatient environment not just “in an outpatient setting.....” To state this, limit their use and the scope of this document.</p> <p>Proposed change (if any): Remove “in an outpatient setting”</p>	The text has been revised in accordance with other comments.
110	L58	14	<p>Comment: The term professional is used on its own and seems quite unspecific.</p> <p>Proposed change (if any):</p> <p>Would suggest changing the term ‘professional’ to ‘health care professional’.</p>	The text has been revised in accordance with other comments.
111	L60	14	<p>Comment: This guidance should not in general always refer to "DDC" when talking about requirements e.g. for integral DDCs acc. to article 1(9) MDR) it must be distinguished between the device constituent and the drug constituent. A NBOp will refer to the intended use of the device constituent and therefore include the use of it with the drug product.</p>	The comment is acknowledged. The text has been reviewed for consistency but there will always be some aspects where the NB and CA will review the same data from different perspectives.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
112	L61	14	<p>Comment: Perhaps it is a grammatical point but the way this sentence is written, it implies an Integral DDC is meeting both the 2nd sub-paragraph of Article 1(8) and the 2nd sub-paragraph of Article 1(9) but Integral DDCs can be products meeting either sub-paragraph condition and do not meet both. Note: A similar description is in the EMA Q&A guidance so perhaps EMA would clarify this in both documents.</p> <p>Proposed change (if any):</p> <p>Integral DDCs are products falling under the second sub-paragraphs of Article 1(8) or falling under the second sub-paragraph of Article 1(9).</p>	The text has been revised in accordance with the comment.
113	L61	14, 19	<p>Comment: The text supporting explanation of Integral and Non-integral DDCs is not clearly structured.</p> <p>Proposed change (if any):</p> <p>Add heading 1.1 Integral DDCs</p>	Adding headings was considered, however not deemed to be necessary due to the conciseness of this guideline section.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
114	L61-97	19	<p>Comment: Given the broad scope of the guideline, it may be more helpful to specifically provide four sets of examples.</p> <p>Proposed change:</p> <p>Provide descriptions and examples of;</p> <p>Article 1(8) integral</p> <p>Article 1(8) non-integral</p> <p>Article 1(9) integral</p> <p>Article 1(9) non-integral</p>	The proposal could be considered for a future revision of the guideline, when there is more experience with the different types of products.
115	L64	14	<p>Comment: The text is unclear in how it is currently written, it does not fully align with MDR.</p> <p>Proposed change (if any): Recommend it be rewritten or copy from MDR 2017/745.</p>	See response to comment 116.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
116	L64, L67 and L82	14	<p>Comment: Line 64 specifically refers to devices 'placed on the market OR put into service'. Line 82 uses terminology 'not physically integrated during manufacturing'. Line 67 overlooks to clarify a similar concept.</p> <p>It is fundamental for industry and Notified Bodies to clearly delineate between integrated products and co-packed products. [Notified Bodies have been known to (even recently) present that certain co-packed products (e.g.: pre-filled syringe with co-packed injection needle) to be single integral. Industry does not agree.]</p> <p>Proposed change (if any): In line 67-69, clarify the EMA interpretation of 'single integral product' in the context of as distributed; or at the point of use or put into service.</p>	The guideline text has been revised to clarify.
117	L64-66	19	<p>Comment: The text used does not accurately represent the MDR text.</p> <p>Proposed change:</p> <p>Use the exact text from the MDR articles.</p>	The guideline text has been revised to clarify.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
118	L64, L67 and L82	19	<p>Comment: Line 64 specifically refers to devices 'placed on the market OR put into service'. Line 82 uses terminology 'not physically integrated during manufacturing'. Line 67 overlooks to clarify a similar concept.</p> <p>It is fundamental for industry and Notified Bodies to clearly delineate between integrated products and co-packed products. [Notified Bodies have been known to (even recently) present that certain co-packed products (e.g.: pre-filled syringe with co-packed injection needle) to be single integral. Industry does not necessarily agree.]</p> <p>Proposed change (if any):</p> <p>In line 67-69, clarify the EMA interpretation of 'single integral product' in the context of as distributed; or at the point of use.</p>	The guideline text has been revised to clarify.
119	L64-66	14	<p>Comment: Edit for clarity – the current wording is not clear regarding Mode of Action (MOA) and needs better distinction to ensure ancillary DD products are not included here.</p> <p>Proposed change (if any):</p> <p>1. Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product, provided that the action of the substance is principal (Article 1(8) MDR), and out of scope are devices performing the primary mechanism of action and the medicinal product is ancillary.</p>	The scope has been revised and this has been adequately revised in the scope section.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
120	L66	14	<p>Comment: Reference seems incorrect as only one of two subparagraphs of Article 1(8) is applicable. It is recommended to be specific to avoid any confusion.</p> <p>Proposed change (if any):</p> <p>...action of the substance is principal (second sub-paragraph of Article 1(8) MDR)</p>	The suggestion has been implemented.
121	L66	14	<p>Comment: The term principal is used on its own and seems quite unspecific.</p> <p>Proposed change (if any):</p> <p>Would suggest changing the term 'principal' to 'primary mode of action'.</p>	The use of "principal mode of action" is in accordance with the MDR. The current wording is retained.
122	L68	14	<p>Comment: Reference seems incorrect as only one of two sub-paragraphs of Article 1(9) is applicable. It is recommended to be specific to avoid any confusion.</p> <p>Proposed change (if any):</p> <p>"...and which if used separately is not reusable (second sub-paragraph of Article 1(9) MDR)."</p>	See response to comment 121.
123	L70	14	<p>Comment: Please include additional, common examples. For example, it would be helpful to clarify if single or multi-dose pre-filled cartridges designed to work with an infusion pump (where the cartridge is not re-usable) are considered DDCs, or container closure systems.</p>	<p>The classification of a product as DDC (or not) is determined by the classification of the medical device component if it were to be considered on its own.</p> <p>On their own, cartridges, which have not been assembled in a delivery device are not considered to be medical devices.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
124	L70	14	<p>Comment: Suggest including Pressured metered dose inhalers (pMDIs) as an example of integral DDC.</p> <p>Proposed change (if any): Addition of: Pressurised metered dose inhalers that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken.</p>	The suggested example has been added.
125	L70-72	24	<p>Quote</p> <p>Examples of medical devices in integral DDCs→</p> <p>"...e.g. e.g. the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays"</p> <p>Comment</p> <p>Dropper or pump systems are no medical devices as they are not intended for the purpose defined in Article 2.</p> <p>The manufacturer of such container closure systems does not perform a conformity assessment procedure.</p> <p>The suitability of container closure systems for medicinal products are assessed during the registration procedure (uniformity of dosage forms) by the National Authorities.</p> <p>Proposed change</p> <p>To avoid double regulation, we propose to amend this section and to delete the example.</p>	<p>The list of examples given in the guideline is not intended to be exhaustive.</p> <p>A container with a dosing and delivery function is regarded as device (part).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
126	L70-80	3	<p>Comment: Clarification is needed which categories of patches/plasters are affected by this guideline. The European Pharmacopoeia specifies medicated plaster (Ph. Eur. 04/2010:0132), cutaneous patches (Ph. Eur. 04/2010:0132) and transdermal patches (01/2008:1011). It is unclear if all these categories are applicable for this guideline or if only patches that are intended to deliver the active substance(s) to the systemic circulation are meant. This should be clearly defined in this guideline.</p> <p>Proposed change (if any):</p> <p>Add definite examples in this section of patches / plasters whose primary mode action is achieved via the medicinal product e.g. transdermal drug delivery patches.</p>	All Ph. Eur. monographs are within scope of the guideline.
127	L70-80	9	<p>Comment</p> <p>The list contains examples, including a DPI (dry powder inhaler), but leaves out some other important and distinct drug-device combinations, such as pMDIs.</p> <p>Proposed Change:</p> <p>Include pressurised metered dose inhalers, i.e., :</p> <p>Dry powder inhalers and pressurised metered dose inhalers that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken.</p>	See response to comment 124.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
128	L70-80	14	<p>Comment: Clarity is required regarding some examples. For instance, in the case of single dose pre-filled syringes, if non-attached needles are co-packaged (see copy/paste from EBE comments to EMA Q&A below):</p> <ul style="list-style-type: none"> A pre-filled syringe (luer lock syringe containing the medicinal product) and a CE-marked needle are provided separately but co-packaged. In one case, EMA advised the Marketing Authorisation Applicant that the pre-filled syringe would be considered an integral medical device and subject to MDR Article 117 and the needle provided separately (in the outer packaging of the medicinal product) was considered non-integral and co-packaged. <p>However, industry considers that a pre-filled syringe co-packaged with a separate (non-integral) device does not constitute a single integral product but is a drug device combination product. Without the needle attached to the pre-filled syringe, it is not ready for use and cannot be considered single integral.</p> <ul style="list-style-type: none"> A medicinal product provided in vials and co-packaged with a pre-filled syringe containing a solution used for dilution (solvent): Will this pre-filled syringe be considered as a co-packaged product and out of scope of MDR Article 117? 	<p>Product classification is not within the scope of this guideline.</p> <p>Bullet point 1: "Integral" refers to the point of "placing on the market", therefore a co-packed needle is non-integral. Since a needle is defined as a medical device (see MEDICAL DEVICES: Guidance document – Classification of medical devices), a medicinal product in a pre-filled syringe co-packaged with a stand-alone needle is considered a non-integral DDC from the perspective of the needle and an integral DDC from the perspective of the syringe.</p> <p>Bullet point 2: Reference is made to the updated Q&A (June 2021) on the MDR implementation.</p>
129	L70-80 and L90-97	14	<p>Comment: Section 1 defines several examples. It should be made clear that the 'designation' of these examples supersedes any conflicting information in current MEDDEV guidances.</p>	<p>Product classification is not within the scope of this guideline, therefore the examples provided cannot take precedence over other relevant legislation and guidance.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
130	L70-80 and L90-97	19	<p>Comment: Examples are always useful. However, the examples provided are only stating what is in scope of the definition.</p> <p>Proposed change:</p> <p>Identify examples that are not integral or non-integral DDCs and are to be considered (only) primary packaging, container closure or medicinal product.</p>	Product classification is not within the scope of this guideline. The examples provided are examples of integral and non-integral DDC and it is not appropriate to include an exhaustive list within this guideline.
131	L70-80 and L90-97	19	<p>Comment: Terms used are not aligned with EDQM terminology.</p> <p>Proposed change:</p> <p>Given the later reference to EDQM, it would be very useful to use the associated EDQM term in conjunction with the listed examples.</p>	The comment is acknowledged.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
132	L70-80 and L90-97	19	<p>Comment: Pressurised Metered Dose Inhaler (pMDI) is notably missing from the example lists. As a very common format, this should be included.</p> <p>Proposed change:</p> <p>Place pre-assembled, non-reloadable pMDI and unassembled or reloadable pMDI into appropriate sections per MEDDEV guidance.</p>	pMDI have been included in the examples list. Refillable/reusable devices are used as an example, the list is not intended to be exhaustive.
133	L70-80 and L90-97	27	<p>Comment: EFA proposes that the list of examples also highlights nasal sprays (integral), epicutaneous patches (integral) and Portable Oxygen Concentrators (non-integral), the use of which is expanding, among others thanks to information made available by national patient associations.</p> <p>Proposed change (if any):</p> <p>For lines 70-80 (integral)</p> <ul style="list-style-type: none"> ▪ Devices for delivery to site of action e.g. the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays, nasal sprays ▪ Single dose pre-filled syringes, pens and injectors ▪ Multi-dose pens and injectors containing a pre-filled cartridge where the cartridge cannot be replaced, and the pen is not designed for subsequent use with a new cartridge ▪ Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets 	It is not within the scope of this guideline to provide advice regarding product classification. The list of examples is not intended to be exhaustive.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> ▪ Dry powder inhalers that are assembled with the medicinal component and ready for use with single or multiple doses but cannot be refilled when all doses are taken ▪ Implants containing medicinal products whose primary purpose is to release the medicinal product ▪ Medicinal products with an embedded sensor ▪ Epicutaneous patches <p>For lines 90-97 (non-integral):</p> <ul style="list-style-type: none"> ▪ Oral administration devices (e.g. cups, spoons, syringes) ▪ Injection needles and filter needles ▪ Refillable pens and injectors (e.g. using cartridges) ▪ Reusable dry powder inhalers; spacers for inhalation sprays ▪ Nebulisers, vaporisers ▪ Pumps for medicinal product delivery ▪ Electronic tablet dispensers ▪ Portable Oxygen Concentrators 	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
134	L71-80	14, 31	<p>Comment: The list of examples excludes transdermal patches and yet these are noted as needing specifications for adhesion in 347-351. Patches can be considered a dosage form and the integral "device" is not always identifiable.</p> <p>Proposed change (If any):</p> <p>Add transdermal patches to the list in 71-80 for clarity and consistency or consider excluding them as out of scope of Article 117 and deleting their performance testing describe in 347-351.</p>	The list of examples is not intended to be exhaustive.
135	L72	19	<p>Comment: The dropper/mouthpiece examples are likely to cause much discussion and EMA should re-check this categorisation.</p> <p>Often pharma industry has the opinion that if the functionality cannot be exhibited if the item were standalone, then arguably it cannot be considered a device. In the example of a cap and dropper taken separately, it cannot be used. Similarly, a mouthpiece disconnected from the container can have no effective function.</p> <p>Conversely, this can also be said of an autoinjector. If an autoinjector is taken in absence of the inner pre-filled syringe, it cannot function.</p> <p>Proposed change: Review against MEDDEV guidance, and if necessary be more specific with the dropper/mouthpiece example.</p>	<p>The list of examples given in the guideline is not intended to be exhaustive.</p> <p>A container with a dosing and delivery function is regarded as device (part).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
136	L73	19	<p data-bbox="659 384 1367 444">Comment: The use of the term 'pre-filled syringe' requires clarification.</p> <p data-bbox="659 461 1367 613">A staked needle pre-filled syringe is clearly designated as a single integral Medicinal Product. However, many products are presented as a non-staked (e.g. luer-lok) pre-filled syringe with a co-packed injection needle. The designation of this type of product remains unclear:</p> <p data-bbox="659 630 1367 748">If the intended use requires that the needle MUST be fitted, it could be argued that the syringe is not single-integral, since the needle is not attached at the point of distribution, and the overall product is 'Co-packed'. In this case:</p> <ul data-bbox="705 764 1367 1284" style="list-style-type: none"> <li data-bbox="705 764 1367 824">• There is no requirement for either CE-marking or Notified Body Opinion. <li data-bbox="705 841 1367 873">• Article 117 does not apply to the syringe entity. <li data-bbox="705 889 1367 976">• The syringe entity should not carry a CE-mark, to avoid confusion with Medical Device substances in a syringe, e.g. bone cements and fillers. <li data-bbox="705 992 1367 1110">• There is no requirement within Pharmaceutical legislation to confirm the syringe conformity to Annex I, since this requirement is only associated with single-integral products. <li data-bbox="705 1127 1367 1284">• This overall final 'framework' would suggest that the Notified Body Opinion is only triggered for a syringe in the presence of an integrated needle. This seems to overlook several other device functionality aspects of a syringe entity. 	<p data-bbox="1379 384 1911 417">See also comment 128.</p> <p data-bbox="1379 433 1911 699">The MEDDEV states that a syringe without a needle is considered to be a medical device, when on its own. The syringe without the needle still has a medicinal purpose, with the needle. Therefore, a medicine pre-filled in a syringe without a needle is an integral DDC and the device component will be subject to Article 117. The needle will need to be CE marked.</p> <p data-bbox="1379 716 1911 776">Product classification advice is not within the scope of this guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>However, if the intended use allows the syringe to be connected direct to an infusion tubing or injection port without the needle (i.e. the needle is optional and only provided for convenience or specific applications); then arguably the syringe COULD BE considered 'single integral' as presented, on the basis that it may perform its function without additional assembly.</p> <ul style="list-style-type: none"> • The EMA Q&A states that 'If the device is not CE marked and a EU certificate from a notified body would be required if the device was used separately, then the applicant must provide an opinion from a notified body on the conformity of the device part with relevant requirements of Annex I to Regulation 2017/745 as part of the marketing authorisation application.' • The syringe entity should not carry a CE-mark, to avoid confusion with Medical Device substances in a syringe, e.g. bone cements and fillers. <p>For such a configuration, if the (needle-less, and thus non-invasive) syringe were taken separately, this would be a Class I Medical Device and as such under MDR an EU certificate from a Notified Body would NOT be required. In this case:</p> <ul style="list-style-type: none"> • A Notified Body Opinion would NOT be required. • The Manufacturer could self-assess conformity to Annex I. <p>If the syringe WAS considered single-integral AND was graduated or claimed sterile, it is assumed that a Notified</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Body would need to be involved to assess the measurement accuracy or sterility aspects, respectively. However, in this case:</p> <ul style="list-style-type: none"> it is currently unclear whether this Notified Body involvement would be performed as a 'full' Article 117 NBoP; or simply focus on the aspects mentioned. <p>The 'non-integral' / 'co-packed' terms used in the guideline and on the EMA Q&A webpage have the potential to confuse certain parties faced with such a configuration. It must be clear to the industry how to handle configurations incorporating both an 'integrated' entity and a co-packed entity. Specifically to this example, whether a pre-filled, needle-less syringe needs assessing against Annex I, or not. Secondly, it must be clear how to handle sterility and measurement functions in this respect.</p> <p>Proposed change (if any): Qualify the term 'pre-filled syringe'. Further, consider clarifying this particular product configuration.</p>	
137	L73	14	<p>Comment: The use of the term 'pre-filled syringe' requires clarification.</p> <p>A staked pre-filled syringe is clearly designated as a single integral medicinal product. However, many products are presented as a non-staked (e.g. luer-lock) pre-filled syringe with a co-packed injection needle. The designation of this type of product remains unclear. The medicinal product-in-syringe is arguably 'Integral', but the overall product is 'Co-packed'.</p>	See response to comment 136.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>If the intended use requires that the needle MUST be fitted, it can be argued that the syringe is not single-integral. However, if the intended use allows the syringe to optionally be connected direct to an infusion tubing or injection port without the needle; then arguably the syringe is 'single integral' as presented. Note also that certain Notified Bodies have been known to present publicly that such a co-packed configuration is treated as single-integral.</p> <p>Such a pre-filled syringe would be Class I (non-invasive) if used separately, due to the absence of an integral needle. As such it would be Manufacturer-assessed, whilst the separate, co-packed needle as Class II would need CE-marking.</p> <p>A Notified Body involvement in the Conformity Assessment of the needle is clear, but no Notified Body would be involved for the overall product and no Art.117 Notified Body Opinion would be required.</p> <p>However, if the syringe was considered single-integral AND was graduated or claimed sterile, a Notified Body would be involved for Opinion on the measurement accuracy or sterility aspects, respectively.</p> <p>The 'non-integral'/'co-packed' terms used in the guideline and on the EMA Q&A webpage have the potential to confuse certain parties faced with such a configuration, who could then believe that a pre-filled syringe presented without an integral needle would not need assessing against Annex I, which is conflicting with current practice.</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): Qualify the term 'pre-filled syringe'. Further, consider clarifying this particular product configuration.	
138	L73	14, 19	<p>Comment: The applicability of the descriptors 'single dose' and 'pre-filled' to syringes, pens and injectors is not clear.</p> <p>Proposed change (if any):</p> <p>Amend text to ...Single use pre-filled syringes, Single use pre-filled pens, Single use prefilled injectors.</p>	The comment is accepted; the wording has been amended.
139	L73	17	<p>Comment: To reduce the risk of ambiguity in terminology used to describe and/or classify drug-device combinations in the EU, Regeneron recommends adding additional examples of such combinations to this bullet in the list of examples of medical devices in integral DDCs.</p> <p>Proposed change (if any):</p> <p>"Single dose pre-filled syringes, pens, and cartridges; injectors (including autoinjectors)."</p>	A reference to autoinjectors has been added. Cartridges are not used for medicine delivery and are not considered medical devices.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
140	L74	28	<p>Comment: Example related to “electromedicine” is missing and clarifications needed.</p> <p>Proposed change (if any):</p> <p>Edit to read:</p> <ul style="list-style-type: none"> • Multi-dose Needle Injection System containing a drug-filled cartridge where the cartridge cannot be replaced, and the pen is not designed for subsequent use with a new cartridge • Single use infusion pump eventually including a blood glucose sensor where the drug reservoir is integrated into pump unit 	The comment is acknowledged. The list of examples is not intended to be exhaustive. No revision has been made.
141	L77-78	3	<p>Comment: other types of inhalers (i.e. metered dose inhalers) might also be considered integral DDCs,</p> <p>Proposed change (if any):</p> <p>Dry powder Inhalers (such as dry powder inhalers, metered dose inhalers or any other inhaler types) that are assembled...</p>	Metered dose inhalers have been added to the list of examples. A reference to “any other inhaler types” has not been added as the list of examples is not intended to be exhaustive.
142	L77	14	<p>Comment: It is recommended to add “pre-assembled” to make it a specific example for an integral DDC.</p> <p>Proposed change (if any):</p> <p>Dry powder inhalers that are assembled pre-assembled with the medicinal component and ready for use...</p>	The wording has been changed in accordance with the comment.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
143	L80	14	<p>Comment: Medicinal products with embedded sensor is unlikely to be a DDC. Does it refer to “smart packaging” elements used to monitor compliance such as sensors that indicate when a product is opened or used? The sensor might be used to record administration data but not intend to administer the medicinal product.</p> <p>Proposed change (if any): Remove or specify</p>	The list of examples is not intended to be exhaustive. It is not within the scope of this guideline to provide classification advice. The wording has been revised for clarity.
144	L80	18	It would be helpful if an example of a medicinal product with embedded sensor could be provided.	See the response to comment 143.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
145	L80	19	<p>Comment: It is unclear whether the perspective being taken by EMA is the 'embedding' or the presence of the sensor. More fundamentally, the sensor purpose would be fundamental to whether it would be considered having device functionality.</p> <p>Proposed change:</p> <p>Provide example of when the sensor would make the MP fall within a DDC definition, and when it would not.</p>	See the response to comment 143.
146	L81	14	<p>Comment: In general, the guideline seems to switch around with the use of the following terms: "component", "constituent" (see line 110), "part" (see line 143).</p> <p>Recommend consistency in the terms or perhaps at the outset state what these terms mean or will be used interchangeably. Refer also to the comment for lines 44-47.</p>	The comment is acknowledged, and the wording has been revised to harmonise definitions.
147	L81	14, 19	<p>Comment: The text supporting explanation of Integral and Non-integral DDCs is not clearly structured</p> <p>Proposed change (if any):</p> <p>Add heading 1.2 'Non-integral DDCs'</p>	Adding headings was considered, however this was not considered necessary due to the conciseness of this guideline section.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
148	L81-97	3	<p>Comment: Regarding the definition of non-integral drug-device combination – products such as infusion bags (not packaged with the medicine but mentioned in the product information (with regards to compatibility of the materials) without specifying the brand etc..) should not be considered under the scope of this guideline.</p> <p>Proposed change (if any):</p> <p>It is therefore suggested to add examples for devices used with a medicinal product or a DDC that are not considered a DDC component.</p>	The comment is acknowledged; however reference is made to Section 6.2 of the guideline, in which requirements for non-integral DDCs with separately obtained devices are outlined.
149	L81-83	7	<p>Proposed change (if any): Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are physically combined for administration.</p>	The proposal was considered however could not be implemented. Non-tangible medical devices (such as software) cannot be physically combined. The wording has been revised for clarity.
150	L81-83	7	<p>Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are combined for administration. The “use” mentioned elsewhere in the guideline is restricted here to the administration only.</p> <p>The guideline should define that “use” means “administration” procedure</p>	The comment is acknowledged. However, it is considered that the meaning of “use” is implicit. Also see response to comment 149.
151	L81-87	22	<p>Proposed Change: Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and medical device(s)) are not physically integrated during manufacturing but where the finished</p>	The comment is acknowledged and the text in the introduction has been revised for clarity.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>medicinal product and the specific finished device(s) are combined for administration by the user at the time of use.</p> <p>Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal product, or where the Non-integral DDCs may take either of two forms. (1) The medical device is supplied to the user in the same package as the medicinal product (co-packaged), therefore forming a unique combination for the safe and effective delivery of the medicinal product. (2) The medical device and medicinal product are obtained separately, but the medicinal product information (SmPC and Package Leaflet) refers to one specific finished medical device, identified by its brand and type, that must to be used to ensure the safe and effective delivery of with the medicinal product but the device is obtained separately. If the medicinal product information refers to a general type of medical device (i.e. infusion pump) or a specific device that may come from many manufacturers (i.e. 2 mL syringe or 29 gauge hypodermic luer needle), it is not a DDC and this guidance does not apply. In eitherall cases, devices not integrated with the medicinal product (i.e. not falling within the scope of Article 1(8) and 1(9) of the MDR) should be CE marked.</p> <p>Rationale: PDA strongly suggests that EMA provide clearer language to help industry understand when a particular pairing rises to the level of "non-integral DDC." In many situations, a device may be recommended for use with a particular medicinal product, but with sufficient flexibility in device choice that the combination cannot be considered a DDC. In PDA's view, EMA's language in line 86 regarding "specific device to be used with the medicinal product" does not provide adequate clarity for industry to determine the</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			combinations that are and are not non-integral DDCs. In our proposed revision, we have attempted to capture the key elements of safe and effective delivery of the medicinal product.	
152	L81-83, L84-89 and L465-470	20	<p>Comment: The definition of a non-integral DDC should provide a clear scope in the cases where the device is obtained separately. A medicinal product may require the usage of device(s) obtained separately to properly administer the drug solely by its nature (e.g. infusion bags, tubes, canules etc.) without these being specified in the Product Information and any product of the required devices may be used.</p> <p>Proposed change (if any):</p> <p>Please clarify if medicinal products fall into the definition of "non-integral DDC" by virtue of a general device or devices used to administer the product, or only where the Product Information makes reference to the use of a specific device product, e.g. trade name.</p>	The comment is acknowledged, the text has been revised, see also comment 151.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
153	L83	28	<p>Comment:</p> <p>For "Non-Integral" DDC's the term "combined for administration" becomes central. As scope of guidance includes device components needed for use of the medicinal product (Line 47) guidance would improve if term is defined or eliminated because "combined" carries uncertainty. For example, an app on a mobile phone that will control delivery the drug would be considered a Non-Integral DDC, i.e. it is a medical device component that should be adequately controlled</p> <p>Proposed change (if any):</p> <p>Add new definition to chapter 10:</p> <p>Combined for Administration means connected to the extent that combination will influence administration performed by the DDC:</p> <ul style="list-style-type: none"> - Physically e.g. via a wire or a catheter - Chemically e.g. one compound that is not a drug will trigger a medicinal product - Optically e.g. light source will initiate delivery of medicinal product - Wireless e.g. radio connected or RFID 	The comment is acknowledged and is considered useful. The guideline has been revised to clarify that "integral" and "non-integral" refer to how the combination is being placed on the market (see response to comment 149).

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
154	L84-89	18	<p>Comment: It would be good to introduce the terminology of Cross-labelling when referencing situations where the Product Information refers to a specific device</p> <p>Proposed change (if any):</p> <p>Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal product, or where the Product Information (SmPC and Package Leaflet) refers to a specific device to be used with the medicinal product but the device is obtained separately (Cross-labelled).</p>	The comment is acknowledged; however the proposed terminology is a US term and is not recognised in the EU. No change to the text has been made.
155	L85	14	<p>Comment: Product Information is being limited to SmPC and Package Leaflet, whilst Patient Information Leaflet, device Instructions for Use, and device specific Investigator Brochure are not being considered as Product Information.</p> <p>Proposed change (if any): Would suggest changing '(SmPC and Package Leaflet)' to '(SmPC, Patient Information Leaflet, device Instructions For Use, and device Investigator Brochure)'.</p>	The comment is acknowledged, but not endorsed. Clarification on this has been included in the appropriate product information sections of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
156	L85	19	<p>Comment: It is not clear why SmPC and Package Leaflet are used here but not PIL, IFU, Quick guide, Investigator Brochure, etc – all of which could refer to a/another specific device.</p> <p>Proposed change: Elaborate or clearly make these examples.</p>	The comment is acknowledged, the text relates to the medicinal product-related information. See also comment 155.
157	L85-86	31	<p>Comment: Non-integral DDCs include those where “the Product Information (SmPC and Package Leaflet) refers to a specific device to be used with the medicinal product but the device is obtained separately”. This one-way labelling is not consistent with how cross-labelled combination products are considered in the United States (i.e. mutually conforming labelling of the medicinal product and device).</p> <p>Proposed change: To harmonize combination product definitions between the US and the EU and to aid in lifecycle management of dossiers, recommend altering the language to reflect mutually conforming labelling between the medicinal product and medical device.</p>	The comment is acknowledged; however, this is outside the scope of this EU guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
158	L86-87	14, 31	<p>Comment: Devices in the first subparagraph, integral or non-integral, should be CE marked (these are the devices where the primary mode of action (PMOA) is the device). Therefore, it should be specified in the guidance that it is the second paragraph that speaks to medicinal PMOA that applies.</p> <p>Proposed change (If any): In either case, devices not falling within the scope of the second subparagraph of Article 1(8) and 1(9) of the MDR should be CE marked.</p>	The comment is accepted, the text has been revised.
159	L86-87, L158 and L550-555	30	<p>Comment:</p> <p>In lines 86-87 and 158, the guideline states that Non-integral DDC's should be CE marked. In class I devices, usually there will not be involvement of Notified Body and manufacturer self-declare the conformity and affix CE mark, where as in risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III), a Notified Body is involved for the CE marking process.</p> <p>Does the agency expect the applicant that all of the below typical components of Non-integral DDC's be CE marked? Please confirm.</p> <ol style="list-style-type: none"> 1. Safety-Needle (Class-IIa) 2. Vial Access device (Class-IIa) 3. Syringe with tip-cap (Class-Is) 4. Plunger-stoppers (Class-Is-if procured sterile) 5. Plunger rod (Class-I) 6. Backstop (Class-I) 	The comment is acknowledged; however, classification is outside the scope of this guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>If yes, then the below proposed changes are suggested in the guideline for better clarity.</p> <p>If answer is no, then the guidance should mention for which components, CE marking is mandatory.</p> <p>Proposed change (if any):</p> <p>If CE marking is required for all the components of a Non-Integral DDC's, then lines 550-555, 86-87 and 158 of the guidance should include the term "device(s)" which denotes all the components of Non-Integral DDC's.</p>	
160	L90	19	<p>Comment: This list is misleading. The items listed are not DDCs in any sense. They are only the device constituents of DDCs.</p> <p>Proposed change:</p> <p>Provide examples of medicinal products with non-integral devices to demonstrate the overall non-integral DDC configuration.</p>	The comment is acknowledged; the introductory sentence to the list refers to "medical devices in DDCs". No change to the text has been made.
161	L95	9	<p>Comment</p> <p>Alongside "nebulisers, vaporisers", please add "accessory" devices – such as mouthpieces and facemasks - to make it clear that they are also covered by the guidance as non-integral DDCs.</p> <p>Proposed Changed Text</p> <p>Nebulisers, vapourisers, mouthpieces, facemasks</p>	The comment is acknowledged; however, this list of examples is not intended to be exhaustive. No change to the text has been made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
162	L96	14	<p>Comment: This example could be misleading. If a pump is prefilled it would be an integral Drug-Device Combination (DDC).</p> <p>Proposed change (if any):</p> <p>“Pumps for medicinal product delivery Reusable or single use pumps which do not contain a medicine when placed on the market”</p>	The comment is acknowledged; the text has been revised.
163	L96	19	<p>Comment: There is inadequate information to qualify that the pump is non-integral. Repatha is one example of non-integral, however there are other examples of pre-filled, pre-assembled, non-reloadable, non-reusable systems that are integral DDCs.</p> <p>Pumps tend to refer to devices that have cyclic delivery function. It may be helpful to also add infusors into this example list to allow industry to recognise other on-body injection systems in the examples.</p> <p>Proposed change:</p> <p>Elaborate Pumps, making clear whether EMA are describing pre-filled, pre-assembled, non-reloadable, non-reusable systems or not.</p> <p>Add Infusors as an example type, making clear whether EMA are describing pre-filled, pre-assembled, non-reloadable, non-reusable systems or not.</p>	The comment is acknowledged; the text has been revised. See response to comment 162. Please note that the list of examples is not intended to be exhaustive.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
164	L97	19	<p>Comment: Software & software apps are not described.</p> <p>Proposed change:</p> <p>Add software and software apps in the list of examples, identifying that subject to their intended use, reusability and the level of integration they may fall into different designations.</p>	The comment is acknowledged; the list of examples is not intended to be exhaustive. It is not within the scope of this guideline to provide classification advice.
165	L97	14	<p>Comment: A tablet dispenser is packaging which has no medical purpose unless the dispensing is intended to deliver the medicine directly to the patient. If it has electronics or moving parts it may be within scope of other legislation. If it were a medical device then it could be an integral DDC if it is not refillable.</p> <p>Proposed change (if any):</p> <p>Remove line 97</p>	The comment is acknowledged; the text has been revised.
166	L97	18	<p>Comment: A electronic tablet dispenser does not meet the definition of a medical device as defined in Article 2, MDR (EU) 2017/745</p> <p>Proposed change (if any):</p> <p>Remove this as an example from the document.</p>	The comment is noted; the text has been revised in relation to comment 165. This is a complex example and there may be instances when dispensers are considered as medical devices. However, since it is not within the scope of the guideline to provide classification advice, the example is removed from the list.
167	L93	23	<p>All dispensing processes should be covered, in particular those used for automated dose dispensing, rather than just devices with electronic parts.</p>	The comment is acknowledged; however, the list is not intended to be exhaustive and the text has not been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>2. SCOPE (L98-123)</u>				
168	L98	22	<p>Comment: PDA suggests that EMA add language to further clarify the scope of this document. We believe that the following language, which could be added at the beginning of the Scope section, matches EMA’s intent.</p> <p>Proposed additional text: This guideline only addresses products where the medical device is specifically intended to administer a medicinal product, whether it is placed on the market in such a way that it forms a single integral product with the medicinal product or is provided as a separate finished medical device which is intended solely for use in the given combination with one medicinal product. It applies only to products for which the medicinal product must be submitted and approved under an MAA. This guideline does not apply to DDC where the medical devices incorporate, as an integral part, a medicinal substance or human blood derivative with a mode of action ancillary to that of the device.</p>	Text added for clarification, but shortened compared to the suggestion. Of note, as per article 1(8) the scope of the guideline is not limited to administration devices.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
169	L99-103	10	<p>Comment: If reference is made to Article 1 (8) in general this would imply that also devices that incorporate an integral medicinal product which only has an ancillary action are in the scope of the guideline (see Article 1 (8) first subparagraph). In addition, Article 1 (9) first subparagraph refers to pure medical devices (delivery devices) and not to DDCs.</p> <p>Proposed change: The references should be updated as follows: "DDCs falling within the scope of Article 1 (9) second sub-paragraph are in the primary focus of this guideline, however, it is recognized that DDCs as defined by Article 1(8) second sub-paragraph of the MDR will likely become more common-place as technology develops. DDCs falling within the definition of Article 1(8) second sub-paragraph of the MDR are within the scope of this guideline and should follow the basic principles"</p>	The comment is acknowledged and text has been added for clarification

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
170	L99-103	24	<p><i>Proposed change</i></p> <p>The references should be updated as follows:</p> <p>"DDCs falling within the scope of Article 1 (9) are in the primary focus of this guideline, however, it is recognized that DDCs as defined by Article 1(8) second sub-paragraph of the MDR will likely become more common-place as technology develops. DDCs falling within the definition of Article 1(8) second sub-paragraph of the MDR are within the scope of this guideline and should follow the basic principles..."</p> <p>If reference is made to Article 1 (8) in general this would imply that also devices that incorporate an integral medicinal product which only has an ancillary action are in the scope of the guideline (see Article 1 (8) first subparagraph).</p>	The comment is acknowledged, the text has been modified for clarification.
171	L99-107	14	<p>Comment: The scope should present that also non-integral DDC are within the scope of the guideline.</p> <p>Proposed change: add non-integral DDC to the scope</p>	The comment is acknowledged, the text has been modified for clarification.
172	L99-107	23	The weakness of the regulatory framework for medical devices must in no way lower the standards EMA imposes on medicinal products.	The comment is noted.
173	L101	31	<p>First subparagraph of Article 1(8) relates to integral devices in which the drug substance is ancillary, and those devices are out of scope of 2001/83/EC, therefore Article 117 does not apply.</p> <p>The guideline is focused on medicinal-led DDCs, and those integral devices within the definition of the second subparagraph of Article 1(8)</p>	The comment is acknowledged, the text has been modified for clarification.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
174	L103	14	<p>Comment: Text refers to 'certain elements' of the guidance not being applicable. The specific elements should be elaborated to avoid misinterpretation or confusion.</p> <p>Proposed change (if any): Clarify which elements are not applicable.</p>	The comment is acknowledged, the text has been modified for clarification.
175	L103	19	<p>Comment: Text refers to 'certain elements' of the guidance not being applicable. The specific elements should be elaborated to avoid misinterpretation or confusion.</p> <p>Proposed change (if any): Clarify which elements are not applicable.</p>	The comment is acknowledged, the text has been modified for clarification.
176	L103-105	8	<p>So far the MDR is concerned, the manufacturer of the device in question is the entity, who is responsible for the compliance with the regulatory requirements. For this reason, it seems necessary to specify who is eligible to seek scientific advice and who is recommended to participate in such scientific advice procedures. Not only pharmaceutical players, but also NB and the device manufacturer should also take their role and responsibility in this process, where appropriate. See general comment above.</p>	The comment is acknowledged. A device manufacturer could apply for a general scientific advice. However, in the context of a DDC, the drug manufacturer retains overall responsibility (scientific advice on product specific questions).

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
177	L108-110	3	<p>The EMA released a Q&A document on Implementation of the MDR and IVDR re the implementation of article 117 of the MDR (EMA/37991/2019). However, this guidance is more focused on integral devices and therefore, clarification on the impact/expectation of this guidance on the life-cycle management of non-integral DDC approved under previous regulations would be required.</p> <p>Furthermore, it is proposed to reference the Q&A document on Implementation in this Guideline on Quality Requirements for drug-device combinations.</p>	<p>The comment is acknowledged. While the lifecycle of the device is under the scope of the MDR, the impact of changes on the non-integral DDC is addressed in this GL in section 8.</p> <p>The Q&A is not referenced in the text in order to future-proof the guideline.</p>
178	L108-110	5	<p>It is outlined that "This guideline covers <u>specific quality dossier requirements to be provided for in an MAA</u> and subsequently during the product lifecycle for integral and non-integral DDCs, as defined in the introduction."</p> <p>Based on this statement, the guidance document is applicable for MAA only; documentation requirements for the NBOP may be individually defined by the respective Notified Body.</p> <p>Is this understanding of the statement correct?</p> <p>If not, please specify the statement.</p> <p>Proposed change (if any):</p> <p>Add statement on Notified Bodies' rights as outlined in the comment or change sentence to clarify the message.</p>	<p>The comment is acknowledged. The guidance document exclusively refers to dossier requirements for MAA.</p> <p>Documentation requirements for the NB opinion is the responsibility of the NBs.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
179	L108-111	14	<p>Comment: It is not clear whether the guideline will apply retrospectively to drug-device combinations that are already on the market and are not subject to variations to the filed information.</p> <p>Proposed change: clarify the context of applicability of the guideline and align with the EMA Q&A published in Feb'19.</p>	The comment is acknowledged, the text has been modified for clarification and the stakeholder is referred to the Q&As on the implementation of the Medical Devices and In Vitro Diagnostic Medical Device Regulations ((EU) 2017/745 and (EU) 2017/746).
180	L110	14	<p>Comment: Biocide regulation is currently being implemented. It would be useful to additionally clarify the applicability of this guideline to biocides.</p> <p>Proposed change (if any): Clarify applicability (or not) to biocides.</p>	There is nothing unique about biocides that needs to be mentioned as part of this guideline. The regulation of biocides is out of scope of this guideline.
181	L110	19	<p>Comment: Biocide regulation is currently being implemented. It would be useful to additionally clarify the applicability of this guideline to biocides.</p> <p>Proposed change (if any): Clarify applicability (or not) to biocides.</p>	The regulation of biocides is out of scope of this guideline.
182	L110	31	<p>Propose to align with MDR text:</p> <p>applies to any DDCs where the containing a medicinal product constituent is either a chemical, biological or radiopharmaceutical as defined in point 2 of Article 1 of 2001/83/EC.</p>	The comment was considered but not incorporated. The intent was to clarify that the requirements apply irrespectively of the nature of the medicinal product

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
183	L112	14, 19	<p>Comment: Please spell out the full abbreviation for clarity.</p> <p>Proposed change (if any): With respect to advanced therapy medicinal products (ATMPs), this guideline...</p>	Comment accepted, text has been adapted
184	L112	31	<p>Comment:</p> <p>1394/2007 ATMP regulation references the MDD and requires an NB assessment of the medical device part. ATMPs also require a dossier according to 2001/83/EC, and article 117 would fulfil this requirement for device components after MDD ceases.</p> <p>Proposed change:</p> <p>Update 1394/2007 to refer to the MDR in lieu of MDD.</p>	The comment is acknowledged, however the proposed action is not within the scope of this guideline.
185	L112-113	18	<p>Comment:</p> <p>Reference to ATMPs and the applicability of this guideline to "<i>devices that are considered part of the container closure system</i>" is not clear and confusing without an example of such a product. Regulation 1394/2007 does define a combined advanced therapy medicinal product within Article 2(d) as incorporating "<i>as an integral part one or more medical devices</i>" and Article 9 details the process and potential NB involvement</p> <p>Proposed change (if any):</p> <p>Remove reference to "<i>devices that are considered part of the container closure system</i>"</p> <p><i>With respect to ATMPs, this guideline applies only to devices that are considered part of the container closure system, or medical devices that are co-packaged or referenced in the</i></p>	The comment has been acknowledged and the text has been modified.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<i>Product Information and obtained separately. Article 117 of the MDR does not apply to ATMPs.</i>	
186	L112-114	8	<p>Comment:</p> <p>The fact that a separately obtained device is mentioned in the Product information should not be sufficient for the request of additional information in accordance with this guideline. The current wording may lead to the impression, that each injectable product (even when it is presented in a multiple-dose vial with rubber stopper) needs to mention in future a specific syringe or injection system in the Product Information with the consequence to provide further data on the recommended device.</p> <p>This understanding would lead to highly undesired specificity on the market regarding syringes, needles and pharmaceutical products. Because in accordance with this guideline, such combinations can be considered as non-integral combination products, too. We suggest that the author of this draft guidance would like to emphasise, that additional data according this guideline are required, where a specific device is mentioned in the Product Information, where the authority anticipates, that the performance parameter of the device may substantially impact the quality, safety and/or efficacy of the whole combination product.</p> <p>Proposed change (if any):</p> <p>With respect to ATMPs, this guideline applies only to devices that are:</p>	The comment is acknowledged. The text has been clarified.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> • considered part of the container closure system, or • medical devices that are co-packaged or • separately obtained devices which are referenced in the Product Information because of their potential impact on the quality, safety and/or efficacy of the whole combination product and obtained separately. <p>Article 117 of the MDR does not apply to ATMPs.</p>	
187	L112-114	9	<p>Since Article 117 of MDR does not apply to ATMPs, manufacturers are not required to submit a declaration of conformity with the MAA or to ask for a positive Notified Body opinion of the device constituent prior to submitting the MAA. However, according to line 112, in some cases the guideline provisions apply to the device constituent of an ATMP when it is part of the container closure system. Please clarify if this means that the CTD of an ATMP DDC should include the device constituent information detailed in paragraphs 5 and 6 even if the device constituent won't even be evaluated by a NB.</p>	The comment has been considered and the text has been modified for clarity.
188	L112-114	32	<p>Comment:</p> <p>This section contains the following text:</p> <p>With respect to ATMPs, this guideline applies only to devices that are considered part of the container closure system, or medical devices that are co-packaged or referenced in the Product Information and obtained separately. Article 117 of the MDR does not apply to ATMPs.</p> <p>Proposed change (if any):</p>	The Commission confirmed the non-applicability of Article 117 to ATMPs. The legal reasoning is out of scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Why does not Art 117 of the MDR apply to ATMPs? Should not for example a pre-filled syringe with an ATMP medicinal product be treated the same way as a pre-filled syringe with other type of medicinal product?</p> <p>Please clarify and explain more in detail.</p>	
189	L112-117	10	<p>Comment:</p> <p>For readability purposes be more specific.</p> <p>Propose change:</p> <p>Even though Article 117 of the MDR does not apply to combined ATMPs as defined under Article 2(1)(d) of Regulation (EC) No. 1394/2007, this guideline applies to delivery devices that are considered part of the container closure system of the ATMPs or medical devices that are co-packaged or referenced in the Product Information and obtained separately.</p>	The text has been modified for clarity.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
190	L112-113, L116-117 and L413-417	16	<p>Comment: Chapter 2 Scope list both in scope (row 112-113) and out of scope items such as ATMPs (row 116-117) and additionally ATMPs are addressed in row 413-417.</p> <p>Chapter 2 Scope (row 112-113) states this guideline applies only to devices that are considered PART of the container closure system but rows 413-417 states medical devices that are USED AS container closure system for ATMPs. This could pose interpretation difficulties.</p> <p>As stated in REGULATION (EC) No 1394/2007 (4) ..</p> <p>For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should ALWAYS be regulated under this Regulation.</p> <p>Proposed change (if any):</p> <p>Harmonise wording and provide examples for clarification and how it related to regulation No 1394/2007, see text above.</p>	The text has been amended for clarification. The critical differentiation is between combined ATMP and not-combined ATMP where the device serves as container closure.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
191	L115	7	<p>The following are out of scope of this guideline:</p> <p>(...)</p> <p>f) Medical device referencing use with a medicinal product that is co-packaged or obtained separately but where the medicinal product and the specific device(s) are not physically combined for administration</p>	<p>The comment is not agreed because any medical device co-packaged or specifically referenced in the product information and considered essential for the administration of a medicinal product is within the scope of this guideline. A physical combination is not a requirement of the guideline.</p>
192	L115	10	<p>Comment:</p> <p>Co-packaging may encompass medicinal products with a diluent and a diluent syringe for reconstitution purposes only; a separate syringe would be utilised for administration. Syringes used for reconstitution purposes only are not combined with the medicinal product for administration and would fall outside the scope of the non-integral DDC on lines 81-83. Furthermore, diluent syringes do not meet the definition of a medical device under Article 2(1) of Regulation (EU) 2017/745.</p> <p>Proposed change:</p> <p>The following are out of scope of this guideline:</p> <p>Co-packaged diluent syringes used only for reconstitution of the medicinal product</p>	<p>The diluent is regulated as a part of the medicine.</p> <p>Device qualification falls outside EMA remit. However, reference is made to the updated Q&A (June 2021) on the MDR implementation regarding this specific example.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
193	L115	19	<p>Comment: For integral DDCs, devices that would be Class I if used separately are out of scope of NBOp and CE-marking, and potentially out of scope of other sections of this guideline.</p> <p>Note that Class I devices that are co-packed are <u>not</u> out of scope of most sections.</p> <p>Proposed change: Expand the list of out of scope examples to cover the 'Class I' situation.</p>	The comment is acknowledged, and text has been included in the scope and in later sections of the GL (re. 3.2.R).
194	L115	31	<p>It should be clarified whether MDR Art. 117 apply to Smart Packaging of medicinal products, in which the packaging is embedded with functionality to communicate with a smart device to track compliance regimen of patients.</p>	External consultation may be required as it is not fully clear whether industry's definition of "smart packaging" is aligned with regulatory definitions.
195	L115-123 and L353-354	24	<p><i>Comment</i></p> <p>As stated under comment line 70-72, it should be made clear that container closure systems without measuring function for medicinal products are out of the scope of the guideline</p> <p>Proposed change</p> <p>Add "f) container closure systems without measuring function for medicinal products"</p>	The comment is acknowledged. Packaging that independently is not to be considered as medical device is per definition out of scope of this guideline. If independently classified as medical device, a measuring function is not per se required for the guideline to be applicable

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
196	L116	18	<p>Comment: A combined ATMP as per Regulation 1394/2007 is not limited to the details contained within the brackets i.e. "(where devices are part of the active substance and/or formulation)" and the statement is not clear without the inclusion of examples</p> <p>Proposed change (if any):</p> <p>Remove the sentence contained within the brackets "(where devices are part of the active substance and/or formulation)" or include examples</p> <p>a) Combined ATMPs (where the devices are part of the active substance and/or the formulation).</p> <p>The ATMP Regulation 1394/2007 applies for MAAs for combined ATMPs.</p>	The comment is acknowledged, the text in brackets has been deleted.
197	L118	14, 31	<p>Comment: It is unclear if electromechanical, electronics, and digital components are inside or outside scope of this guideline (line 118 vs line 371). The guideline should cover electromechanical, electronics and digital components. They should be included as they are in scope of MDR and Article 117 if they are part of the device constituent part i.e. pens with electronic dose display shall be in scope. These device components should be under the jurisdiction of the notified body and their assessment is included in the NBOp.</p> <p>Proposed change (if any):</p> <p>Delete line 118</p>	Medicinal products utilising electromechanical devices (including active implantable devices), electronic add-ons and digital elements of devices are in the scope of the guideline where they are expected to impact, even potentially, the benefit-risk assessment of the medicinal product from a quality perspective; however, in this regard, it is acknowledged that more detailed guidance may be required in the future.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
198	L118	19	<p>Comment: Electromechanical components of devices/electronic add-ons are listed as out of scope of this guideline. There is no clarification of why this should be so; and no reference to where relevant guidance CAN be found.</p> <p>Proposed change (if any): Clarify the expectations with respect to electromechanical components.</p>	See response to comment 197.
199	L118	25	<p>Comment: Unclear if electromechanical, electronics, and digital components are inside or outside scope of this guideline (line 118 vs line 371). The guideline should cover electromechanical, electronics and digital components. They should be included as they are in scope of MDR and Article 117 if they are part of the device constituent part. These device components should be under the jurisdiction of the notified body and their assessment is included in the NBOP.</p> <p>Proposed change (if any): Delete line 118.</p>	See response to comment 197.
200	L118	28	<p>Comment:</p> <p>Electromechanical components are not defined. Is that solely devices with actuators? – or is a broader range of products considered?</p> <p>There is a contradiction in bullet b) (out of scope) and “Scope” in terms of “are necessary”. If an electrically driven actuator is integrated into the drug GSPR would apply; however, b) states it is out of scope.</p> <p>Electronic add-ons are not clearly segregated from Electromedical Devices and Accessories with batteries. When is it needed (then in scope) or an add-on – assumed to be not needed</p>	See response to comment 197.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any):</p> <p>Edit to read (out of scope list):</p> <p>b) "(delete first part of b) ... Electronic add-on, i.e. not necessary for use of the medicinal product</p>	
201	L118-119	6	<p>'Electromechanical components of devices (including active implantable devices) and electronic add ons to existing products' are excluded from this guidance. It is not clear which guidance would now apply to these DDC and to which criteria they should be assessed. Moreover this exemption does not seem to be in line with examples given in lines 271 and 371.</p> <p>Proposed change (if any):</p> <p>Provide a reason why or on which aspects listed categories have been excluded.</p>	See response to comment 197.
202	L118-119	9	<p>Original Text</p> <p><i>b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.</i></p> <p>Comment</p> <p>Integral DDC with electromechanical components are common, therefore some guidance in that area would be useful. In fact, the draft guideline mentions "software" (e.g., in lines 273, 371), which presupposes inclusion of at least some electromechanical components.</p> <p>Proposed Changed Text</p>	See response to comment 197.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.	
203	L118-119	18	<p>Comment: It is not understood what the intent was by the inclusion of example" b) Electromechanical components of devices and electronic add-ons to existing products"</p> <p>Proposed change (if any):</p> <p>Remove this as an example</p> <p>b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.</p>	See response to comment 197.
204	L118-119	22	PDA suggests that EMA might clarify what it intends when it refers to "Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products." As written, we believe that this language is very broad.	See response to comment 197.
205	L118-119, L271-272 and L371	16	<p>Comment: Chapter 2 Scope list out of scope items such as Electromechanical components (row 118-119), yet electrical functional components are addressed in 271-272, and communication with software in 371.</p> <p>Proposed change (if any): Keep and develop more guidance text concerning electromechanical drug-device combination products, including connectivity.</p>	See response to comment 197.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
206	L120	23	<p><i>Comment</i></p> <p>It is not clear why the veterinary DDCs are out of scope.</p> <p><i>Proposed change</i></p> <p>Please add clarification to the guideline.</p>	<p>This is a CHMP guideline and therefore guidance is limited to medicines for human use.</p> <p>The potential for guidance on veterinary medicines is a matter outside the scope of this guideline.</p>
207	L121	14	<p>Comment: Please specify that companion diagnostics are included under in vitro diagnostic exclusion.</p> <p>Proposed change (if any): <i>In-vitro</i> diagnostic devices, including companion diagnostics.</p>	<p>The comment has been considered and the text modified accordingly.</p>
208	L122	14	<p>Comment: It is possible that an integral DDC which has a medicine as the primary mode of action could also include one or more ancillary medicines. An example of this would be a heparin-coated IV line or cannula.</p>	<p>The comment is acknowledged, but does not require a revision of the text.</p>
209	L122-123	14	<p>Comment: This item "(e)" is redundant under the out of scope since "Medical devices incorporating as an integral part, a medicinal substance or human blood derivative with a mode of action ancillary to that of the device" are covered by the first subparagraph of Article 1(8) and hence do not meet the conditions already stated in the Introduction section of the guideline defining what is an Integral DDC.</p>	<p>The comment is acknowledged. The section has been modified for clarification.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
210	L122-123	10	If the correct references are made in line 99 - 103 (see comment above), the example "e" ("Medical devices incorporating, as an integral part, a medicinal substance or human blood derivative with a mode of action ancillary to that of the device") could be removed from the list as this is an example for a device according to Article 1 (8) first subparagraph.	The comment is acknowledged. The section has been modified for clarification.
211	L122-123	18	<p>Comment: Amend the definition to align with the MDR wording for devices with ancillary medicinal products and classified as a medical device as per MDR Annex VIII, Rule 14</p> <p>Proposed change (if any):</p> <p>e) Medical devices incorporating, as an integral part, a medicinal substanceproduct or human blood derivative and that has an action ancillary to that of the device as defined by MDR Annex VIII, Rule 14with a mode of action ancillary to that of the device.</p>	The comment is acknowledged. The section has been modified for clarification.
<u>3. LEGAL BASIS (L124-133)</u>				
212	L128-130	14	<p>Comment: Amendment to reflect the actual title of Regulation (EU) 2017/745</p> <p>Proposed change (if any): Regulation (EU) 2017/745 on medical devices (the Medical Devices Regulation or MDR), which amends amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and which repeals repealing Council Directives 90/385/EEC and 93/42/EEC.</p>	The comment is acknowledged. No change to text is made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
213	L128 - 130	18	<p>Comment: Sentence is difficult to read and does not include the repeal of the Active implantable medical device directive 90/385/EEC</p> <p>Proposed change (if any):</p> <p><i>Regulation (EU) 2017/745 on medical devices (the Medical Devices Regulation, MDR).</i></p> <p>Or</p> <p><i>Regulation (EU) 2017/745 on medical devices (the Medical Devices Regulation, MDR) which amends Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, and which repeals Directive 90/385/EEC (the active implantable medical device directive, AIMDD) and Directive 93/42/EEC (the Medical Device Directive, MDD).</i></p>	The comment is acknowledged. The text has been changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
214	L131-133	9	<p>Comment</p> <p>Presumption of conformity to MDR 2017/745 Annex I GSPR is supported by harmonized standards published in the Official Journal of the European Union. In addition, some guidance on establishing compliance to GSPR can be found on the EU Commission website.</p> <p>Proposed Changed Text</p> <p><i>In addition, this guideline should be read in conjunction with all other relevant directives and regulations, the European Pharmacopeia and all relevant Commission, ICH and CHMP guidelines, Q&A documents, <u>list of harmonized standards</u>, and other documents as linked to or published on the EMA <u>and EU Commission's Medical Devices websites</u>.</i></p>	The comment is acknowledged. No change to text is made.
<u>4. GENERAL CONSIDERATIONS (L134-168)</u>				
215	L137	28	<p>Comment: Phrasing is more focused on technology than on risk to the patient</p> <p>Proposed change (if any): Edit to read:</p> <p>The patient risk associated with the device, complexity of the device, relevant patient characteristics and the clinical setting in which the DDC is used are also important aspects of the review process.</p>	The comment is acknowledged; the guideline text has been amended to include reference to 'patient characteristics and user requirements'

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
216	L137-138	19	<p>Comment: DDCs are used by a range of users, not just patients. Patient characteristics may be important, but user characteristics are fundamental to usability.</p> <p>Proposed change: change to User (with a caveat that the user may not always be the patient)</p>	The comment is acknowledged; the guideline text has been amended to include reference to 'patient characteristics and user requirements'
217	L138-139	19	<p>Comment: DDCs are used more broadly than in a 'clinical setting'. Use environments include the clinical setting but are not limited to that and include ambulance, workplace, schools, public settings etc.</p> <p>Proposed change: change to Use Environment to align with HF/UE guidance.</p>	The comment is acknowledged; the guideline text has been amended to include reference to 'the clinical setting or use environment'
218	L138	14	<p>Comment: characteristics and clinical setting – mis-represents this could be a hospital only environment</p> <p>Proposed change (if any): change clinical setting to use setting as this is more-broader and better aligned with standard / understood terms</p>	The comment is acknowledged; the guideline text has been amended to include reference to 'the clinical setting or use environment'
219	L139	14	<p>Comment: Requirements are stated for 'full evaluation of the impact of the device' on several aspects of the product. This is not elaborated or explained. More specific guidance is needed in that respect.</p> <p>Proposed change (if any): Define 'full'; 'evaluation'; impact. Suggest cross-reference to other applicable sections are added (e.g 3.2.P.2.4 and 3.2.P.2.6)</p>	The comment is acknowledged; the guideline text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
220	L139	19	<p>Comment: Requirements are stated for 'full evaluation of the impact of the device' on several aspects of the product. This is not elaborated or explained.</p> <p>Proposed change (if any): Define 'full'; 'evaluation'; impact.</p>	The comment is acknowledged; the guideline text has been amended
221	L140	14, 15, 19	<p>Comment: QTTP (typo)</p> <p>Proposed change (if any): QTTP</p>	The guideline text has been corrected
222	L141	28	<p>Comment: "Control Strategy"</p> <p>Guidance should refer to considerations a manufacturer has to control the DDC. Surely, it cannot be expected, that all changes are to be submitted for evaluation, re-execution of Clinical Trails etc.</p> <p>Adequate control of design and development should be expected</p> <p>Proposed change (if any):</p> <p>When controlling constituent parts of the DDC please refer to ISO 20069 regarding guidance on those considerations needed for the manufacturer when a change is planned, implemented and controlled</p>	The comment is acknowledged; no change to the guideline is proposed as lifecycle management is discussed further in section 8 of the guideline.
223	L142	14	<p>Comment: This is the first mention of Art. 117 for integral DDCs, would expect to see this detail in the introduction/or scope</p> <p>Proposed change (if any): Move some language 142-143 to the scope/introduction</p>	The comment is acknowledged; the guideline text has been amended accordingly (first reference in the introduction).

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
224	L142	14, 19	<p>Comment: This text refers ONLY to MAA, and excludes the Variation aspect Lines 108-110 states applicable to MAA and Lifecycle changes. This should be consistent for clarity.</p> <p>Proposed change (if any):</p> <p>Add lifecycle changes or add a positioning statement early in the document to use the term 'MAA' to always include variations (or variations based upon substantial change to the device part) unless otherwise stated.</p>	The comment is acknowledged; the guideline text has been amended accordingly.
225	L142	14	<p>Comment: This section is being paraphrased instead of being taken directly from the MDR. Please clarify that this is the interpretation and not exact quotation of the MDR text.</p> <p>Proposed change (if any): The interpretation of In accordance with Article 117 of the MDR, is that an MAA for...</p>	The comment is acknowledged, the text has been amended.
226 258	L142-147	14	<p>Comment: Under Article 117, evidence of CE marking according to MDR of the device component of single integral DDCs is required, where available.</p> <p>Demonstration of conformity should be broadened to allow submission of CE mark evidence against the MDD if the device supplier holds a valid EC certificate beyond 26 May 2020.</p> <p>Proposed change (If any):</p> <p>The following text should be added to (1) starting line 145:</p> <p>“Medical devices CE marked against the MDD will still be allowed on the EU market for the time limited</p>	<p>The comment is acknowledged, however, the guideline relates only to the Medical Device Regulation and is not considered applicable for the Medical Device Directive. No change to the guideline is proposed.</p> <p>Reference is also made to the updated Q&A (June 2021) on the MDR implementation.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>period as set out in Article 120 of the MDR, and if the EC certificate is valid.</p> <p>This period of validity for a device’s CE mark should also apply in the context of integral DDCs”.</p>	
227	L142-147	31	<p>Evidence of CE marking to MDR of the device component of integral DDCs is requested, when available, under Article 117. Demonstration of conformity should be broadened to allow submission of CE mark evidence to MDD if the device supplier holds a valid EC certificate beyond 26 May 2020.</p> <p>Medical devices CE marked to MDD will still be allowed on the EU market for a time-limited period if the EC certificate is valid. This period of validity for a device’s CE mark should also apply in the context of integral DDCs.</p>	<p>The comment is acknowledged however the guideline relates only to the Medical Device Regulation and is not considered applicable for the Medical Device Directive. No change to the guideline is proposed.</p> <p>Reference is also made to the updated Q&A (June 2021) on the MDR implementation.</p>
228	L142-153	22	<p>Comment: PDA believes that the text in lines 142-153 could be clarified to reduce confusion. Our suggested revision follows. In addition, PDA suggests that EMA include examples of the types of devices that are addressed by each section, to aid understanding. PDA does not believe that it is entirely clear which integral devices would require involvement of a Notified Body and which would not, if they were not being used separately. In a guideline such as this, examples can be very helpful.</p> <p>The proposed text mentioned CE marking in line 146. We suggest omitting that reference to the CE mark because the CE mark itself is not necessary to show conformity with GSPRs. Because the CE mark is not relevant to the point being made, we suggest referring only to the Certificate of Conformity, which will help avoid confusion.</p>	<p>The comment is acknowledged. The text has been further aligned with the wording of the MDR.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>The issue of CE marking on integral devices itself is a topic that could be clarified. Can integral devices be CE marked? Which types of integral devices may have a Certificate of Conformity? PDA suggests including examples or additional discussion of this topic.</p> <p>Proposed change:</p> <p>In accordance with Article 117 of the MDR, an MAA for an integral DDC shall include evidence of the conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs), as follows: 1. Where available If an EU Declaration of Conformity issued by the device manufacturer or a Certificate of Conformity issued by a Notified Body (NB) that allows a CE mark to be displayed on the device exists, that document is adequate.</p> <p>Otherwise the following evidence may be used:</p> <p>2. If the above information (on results of the conformity assessment) is not available:(a) 1. for medical devices that, if used separately, do not require the involvement of a NB, the applicant’s confirmation that the device part meets the relevant GSPRs. This option would apply to devices that are Class 1 devices (not sterile or having a measuring function), including non-sterile, non-measuring, non-invasive applicators.</p> <p>(b)2. if the conformity assessment of the medical device, if used separately, would require the involvement of a NB (e.g., is Class 1 sterile, Class 1 with a measuring function, Class 2a, Class 2b or Class 3), a Notified Body</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			opinion (NBop) on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB.	
229	L142-153	24	<p><i>Comment</i></p> <p>Article 117 MDR (amending the Annex I of Directive 2001/83/EC) does only foresee a Declaration of Conformity or the Notified Body opinion (NBop) procedure in the case that the product in question would fall under the definition of MDR Article 1 (8) or (9).</p> <p>It is therefore not foreseen to our understanding of the MDR that e.g. dropper inlets, which form a fix connected part of the primary packaging of medicinal products (e.g. eye drops or oral drops), undergo a certification or a NBop procedure.</p>	The comment is acknowledged and full information on the primary packaging is to be supplied in the dossier.
230	L142-153	25, 28	<p>Comment: This section seems not to be fully aligned with MDR Article 117 and we see a risk that it may give confusion rather than clarity. The lines 145-148 appears not relevant, as line 142 says this relates to integral DDC's – and having a CE mark on the device is only applicable for a non-integral DDC not regulated via Directive 2001/83/EC or Regulation (EC) No 726/2004.</p> <p>Proposed change (if any): Delete lines 145 to 148 (this will in essence leave the requirements from MDR Article 117 referring back to the second subparagraph of Articles 1(8) and 1(9) in MDR)</p>	The comment is acknowledged. The text has been further aligned with the wording of the MDR.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
231	L142, L145-147 and L406-407	14	<p>HIGH PRIORITY</p> <p>Comment: It is not clear how the situation of the CE mark applied to the device part of an integral DDC would work in practice as these device parts, by definition, are not Medical Devices. If a single integral Medicinal Product carries a CE-mark this would suggest incorrectly that the product has a Medical Device mode of action. Therefore, it is unclear how the CE mark could legitimately be applied to these device parts.</p> <p>Proposed change (if any): To aid understanding, it would be helpful to include some examples of integral DDCs where the device part is CE-marked.</p>	The comment is acknowledged, and the text has been further aligned with the wording of the MDR.
232	L143	14	<p>Comment: Reference to GSPRs should be more specific and point to Annex I of the MDR and would be consistent with language in the EMA's Q&A guidance.</p> <p>Proposed change (if any): ...conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs) set out in Annex I to Regulation (EU) 2017/745 as outlined in Section 5.4 (3.2.R) as follows:..</p>	The comment is acknowledged, and the text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
233	L145	14	<p>Comment: In contrast to EMA's Q&A guidance for devices (EMA/37991/2019, refer to Table 1), a Declaration of Conformity (DoC) OR the EC certificate of the NB to be submitted with the MAA for integral DDCs (if available) is required. The Q&A guideline requires both a DoC AND the NB certificate.</p> <p>As from an industry perspective an EC certificate is deemed sufficient as evidence for a NB assessment, it is recommended to correct the Q&A guidance respectively.</p>	The comment is acknowledged, and the guideline is aligned with the MDR.
234	L145	19	<p>Comment: This 'option' of a CE-marked device constituent is suggested by Article 117 text within the MDR. However, there is an opportunity here for EMA to clarify the expectations. A Medicinal Product should not be misrepresented as a Medical Device. If a single integral Medicinal Product carries a CE-mark this would suggest incorrectly that the product has a Medical Device mode of action. The CE-mark should be reserved for those products that are a physical Medical Device or for a substance with a physical mode of action.</p> <p>It may be feasible and legally correct that a device constituent may have been taken through a full Conformity Assessment and gain certification entitling the Manufacturer to place a CE-mark upon that product. However, in the case of a single-integral Medicinal Product with medicinal mode of action, my understanding is that a CE-mark should NOT be applied.</p> <p>Another aspect of this is the requirement for UDI on such a device, which conflicts with regulation and guidance on UDI for combined products; and the serialisation requirements for pharmaceutical products. Any UDI that would 'normally' be</p>	The comment is acknowledged, and the text has been further aligned with the wording of the MDR.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>present on the standalone device, must be removed if integrated. The appropriate mechanism/solution for this in UDI databases would need to be checked.</p> <p>Proposed change (if any): Clarify EMA expectations for this option and ensure Industry understands that although a CE-mark entitlement may have been granted, it should not be physically applied.</p>	
235	L145	35	<p>Comment:</p> <p>With reference to the requested documentation, i.e. "an EU Declaration of Conformity issued by the device manufacturer, or a Certificate of Conformity issued by a Notified Body (NB)", we suggest updating the 'and/or' to reflect the different requirements for both cases. Please note that:</p> <p>For CE marked medical devices that do not require the assessment of conformity by a notified body (class I non-sterile, non-measuring, non-reusable surgical) - you should provide the Declaration of Conformity, where this is available.</p> <p>For CE marked medical devices where a notified body assessment of conformity is required - you should provide the Declaration of Conformity and the EU notified body certificate, where available.</p> <p>Proposed change (if any):</p> <p>To clarify the different requirements, as above mentioned.</p>	The comment is acknowledged. The text is aligned with the wording of the MDR.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
236	L145-146	8	We ask to take into consideration: for most devices both documents (Declaration of Conformity and CE Certificate) are only valid in combination as proof of full compliance with the medical device regulations. The exemptions are class I products, which integrate no additional functionality that triggers supplementary assessment by a Notified Body (e.g. measuring function or sterility). Those simple class I devices are subjected to self-certification. And sufficient evidence is provided by the device manufacturer via an EU Declaration of conformity without involving a Notified Body. Therefore, we would suggest for devices, where the conformity assessment requires the involvement of a NB, that the dossier of the combination product contains usually both: the EU Declaration of Conformity and the CE Certificate.	The comment is acknowledged. The text is aligned with the wording of the MDR.
237	L145-147	23	<p>A better option for ensuring that manufacturers comply with European harmonised standards, which would presume conformity with the General Safety and Performance Requirements (GSPRs) for medical devices, would be for an independent third-party certification body (other than one with the role of notified body (NB)) to certify compliance with these standards.</p> <p>It is surprising that EMA considers self-certification by manufacturers compatible with the standards to be met by medicinal products.</p>	EMA does not authorise and regulate medical devices. The requirement for CE (self-) certification of medical devices is underpinned by legislation. Reference is also made to the core precept of this guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
238	L145-147	31	<p>Comment:</p> <p>Clarify that “Where available, an EU Declaration of Conformity issued by the device manufacturer, or a 145 Certificate of Conformity issued by a Notified Body (NB) that allows a CE mark to be displayed on the device part.”</p> <p>CE Mark does not apply to the overall integral product, but only to the device constituent.</p>	The comment is acknowledged, and the guideline text is aligned with the MDR.
239	L149	18	<p>Comment: Inclusion of device classification to clarify scope</p> <p>Proposed change (if any):</p> <p><i>(a) for medical devices that, if used separately, do not require the involvement of a NB, such as a Class I device, the applicant’s confirmation that the device part meets the relevant GSPRs</i></p>	The comment is acknowledged, however, no update to the guideline is proposed.
240	L151-153	21	<p>Comment: To add a proposed indication</p> <p>Proposed change (if any):</p> <p>If the conformity assessment of the device, if used separately, would require the involvement of a NB, a Notified Body opinion (NBOp) on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB. If the device has been manufactured outside the EC the certification of NB should be mandatory.</p>	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
241	L153 and L438	5	<p>It is outlined that the NBO is “issued by an appropriately-designated NB”. (the term is also present in line 412)</p> <p>Line 438: “It should be ensured that the NB is appropriately accredited for the issuance of such an opinion”</p> <p>What does “appropriately-designated” and “appropriately accredited for the issuance of such an opinion” mean? Which aspects of a designation are meant?</p> <p>There is no definition/statement on what is regarded as a “appropriately-designated” NB.</p> <p>Does the appropriate designation refers to the medical device code (see Commission Implementing Regulation EU 2017/2185) which would apply in the case the device component would be CE marked?</p> <p>438: There will be no accreditation for article 117 procedures. The NBs designation should cover sufficient competencies corresponding to the type of the medical device.</p> <p>Proposed change (if any):</p> <p>Provide a definition/statement on the term “appropriately-designated” and/or reconsider the statement by avoiding an undefined term.</p> <p>Please identify the criteria to determine whether the NB is appropriately designated and at what time point this will be verified by EMA/ CA (e.g. during the validation period of the MA submission).</p> <p>Reference can be made to the NANDO website which identifies the designated notified bodies and their scope of</p>	The comment is acknowledged, and the text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>designation including device codes. For Art 117 the following codes can be relevant for the selection of a suitable NB:</p> <ul style="list-style-type: none"> • MDA 0102 Active implantable devices for delivering drugs or other substances • MDA 0307 Active non-implantable respiratory devices • MDA 0309 Active non-implantable ophthalmologic devices • MDA 0318 Other active non-implantable devices • MDN 1202 Non-active non-implantable devices for administration, channelling, and removal of substances, including devices for dialysis • MDN 1206 Non-active non-implantable ophthalmologic devices • MDN 1214 General non-active non-implantable devices used in healthcare and other non-active non-implantable devices • MDS 1010 Devices with a measuring function 	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
242	L153 and L438	14	<p>Comment: Please define “appropriately designated”. Technically the class of a device “if used separately” is hypothetical in the case of integral DDCs. Does this mean a Notified Body designated for the hypothetical type or a Notified Body designated for undertaking NBOps? There is no planned NB accreditation number for DDC. It is unlikely that a MAA will be able to control if a NB has been appropriately designated.</p> <p>Proposed change (if any): Please clarify which Notified Body designation code(s) should be used for this range of products or remove.</p>	The comment is acknowledged, the text has been amended.
243	L153	19	<p>Comment: The reference to an appropriately designated NB reflects the text of the MDR. However, it would be useful for industry to clarify what designation codes the medicines Competent Authority (or Pharma) should use to determine the appropriateness of a particular NB’s designation. This applies especially since there is no NBOG code for drug delivery DDCs covered by MDR Art.1(9).</p> <p>Proposed comment: Elaborate what the Pharma Applicant should submit (if anything) to demonstrate the appropriateness of the NB.</p>	The comment is acknowledged and the text has been amended.
244	L155	18	Move the core precept of the guideline to earlier in the document	The comment is acknowledged, however, no update to the guideline is proposed.
245	L155 et al	19	<p>Comment: Competent Authority can refer to either medicines or medical device.</p> <p>Proposed change:</p>	The comment is acknowledged, the text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Qualify this phrase throughout the document with medicines- or device-.	
246	L155-157 and L162-163	23	EMA must develop independent expertise in medical devices so that it can evaluate and, if necessary, qualify NB opinions on conformity with the GSPRs and usability.	The comment is outside the scope of the guideline. EMA does not authorise or regulate medical devices and reference is made to the core precept of the guideline.

247	L155-157	5	<p>It is outlined that CA will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs.</p> <p>The assessment of the applicable GSPR by non-considering the impact of the medicinal product on the device performance is not conclusive.</p> <p>This term needs further definition. Relevant to the device? Relevant to the NB? For example, a sterile device is GSPR 11 relevant or as this will be looked at by the Competent Authority not-relevant?</p> <p><u>Proposed wording of the lines 155-157:</u></p> <p>It is outlined that CA will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product, and that, as applicable <u>and that the NB will evaluate the medicinal product specific aspects relevant to the quality, safety and efficacy of the medical device.</u></p> <p>Proposed change (if any):</p> <p>Add guidance how to minimise duplication of work between the CA and NB? Following areas of overlap are identified: compatibility of the device (packaging) with the drug under GSPR 10.3, drug/ device interaction (e.g. stability of the drug and device, material interactions, leachables and extractables), functionality (accuracy of dosage), usability. See also Compatibility from line 292 till 310 which overlaps with GSPR 10.3 of Annex I.</p>	<p>The comment is acknowledged, and the guideline has been revised for clarity.</p>
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Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
248	L155-157	6	The guideline does not clarify what are the GSPRs and what are the device specific aspects of safety and performance relevant to quality safety and efficacy of the medicinal product. It would be appreciated if examples for both categories are given for commonly used DDC's.	The comment is acknowledged, however, no update to the guideline is proposed.
249	L155-157	8	<p>The guideline states here clear double assessment of the GSPRs (Annex I of Regulation (EU) 2017/745), because their assessment is already subjected to the regulatory responsibility of the device manufacturer and -where appropriate- to the surveillance by a Notified Body. Therefore, clarity on the assessment strategy employed by the competent authorities is crucial since many Drug-Device combination requirements are already captured as well in the GSPRs. This is particularly true, when we talk about compatibility requirements. Please compare for this reason No. 10.3, 10.4.1, 12.1 of Annex I of Regulation (EU) 2017/745.</p> <p>In this light we also recommend to provide clarity, if the competent authorities will consider for their assessment relevant ISO-Norms (e.g. EN ISO 10993-17:2009 "Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances"), as well. Those standards are harmonised by the commission in order to establish presumption of conformity of medical devices with the GSPRs (see Article 8 of Regulation (EU) 2017/745).</p>	The comment is acknowledged, the text has been amended in the meantime.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
250	L155-157	14	<p>High priority</p> <p>Comment: Most GSPRs are related to device specific aspects which may impact the quality, safety and efficacy of the medicinal product. Therefore, in order to avoid duplicative assessment between CA and NB, clarification is required in relation to the scope of the review of CA and NB to ensure complementary review.</p> <p>Proposed change (if any): The core precept of this guideline is that the Competent Authority for the regulation of medicines (CA) will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs. Wherever there is overlap within the scope of CA and NB assessment, it is suggested that the intended purpose of the device will determine the scope of the assessment by the CA.</p>	The comment is acknowledged, however, no update to the guideline is proposed.
251	L155-157	19	Absolutely agree with this core precept, however pharma industry will likely resist this point. See general points raised above.	The comment is acknowledged, however, no update to the guideline is proposed.
252	L155-157	24	<p><i>Comment</i></p> <p>The assessment of the GSPRs is in the scope of the NB. Therefore, it is unclear why certain results of the GSPRs evaluation should be included into the dossier of a medicinal product.</p> <p>Proposed change</p> <p>Please clarify.</p>	The comment is acknowledged, however, no update to the guideline is proposed. The medicinal product is regulated under Directive 2001/83/EC and assessment is performed in line with this.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
253	L155-157	25	<p>Comment: Clarification of core precept (lines 155-7): The content of the Quality part of the dossier should focus on compatibility of the parts of the DDC in direct contact with the drug product, such as the primary packaging (in alignment with requirements for co-packed medical devices lines 532-3).</p> <p>Information on the secondary packaging with device functionality should be summarized to facilitate understanding of the working principle(s) and assurance of suitability/performance. The assessment of device functionality, safety and performance, is performed by the notified body and documented in the NBOp (in alignment with ambition to avoid duplication of assessment in line 441) It should be possible to adapt the information provided for the DDC in the MAA, provided that this is justified under a risk-based approach (in alignment with requirements for ATMPs lines 188-9).</p>	The comment is acknowledged, and the guideline has been revised accordingly.
254	L155-157	27	<p>Comment: The Competent Authority should evaluate the device-specific aspects of safety and performance that are both relevant and irrelevant to the quality, safety and efficacy of the medicinal product, as in some cases there is the issue of safety and performance of the device independently of the medicinal product. Besides, that sometimes the same device can take different products e.g. some inhalers and nebulizers.</p>	The comment is acknowledged, and the guideline has been revised accordingly.
255	L155-161	14	<p>Comment: Further precision required regarding the acceptable information/justification to support the need for separate non-integral devices; maybe cross-reference to section 6.2 of guideline to be included.</p>	The comment is acknowledged, and the guideline has been revised accordingly to include cross-reference to section 6.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
256	L156	2	<p>“Relevant”</p> <p>In some cases, there is the issue of safety and performance of the inhaler independently of the medicinal product. It should not be forgotten that sometimes the same inhaler can take different products</p>	The comment is acknowledged, however, no update to the guideline is proposed.
257	L156 ++	19	<p>Comment: The text uses a range of terms related to safety, quality, efficacy, performance including:</p> <p>156, 161, 279, 469, 473, 506, 545, 581 quality, safety and/or efficacy</p> <p>179, 465, 604 quality, safety and efficacy</p> <p>156, 501 safety and performance</p> <p>252, 560 (overall) performance</p> <p>277 (functional) performance</p> <p>302, 345 performance</p> <p>517 design and performance</p> <p>558 product performance characteristics</p> <p>579 efficacy or safety</p> <p>586, 607 efficacy and safety</p> <p>The mixed use of and, or & and/or is confusing. In some cases it may be interpreted that the point is only relevant when <u>all</u> of the listed attributes are impacted. The use of two of the three terms in some places suggest that the third is not key to the topic under discussion, etc.</p>	The comment is acknowledged, and the text has been reviewed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Additionally, I would like to see 'usability' added to these collective terms given the significant impact of usability on the overall effectiveness of a combined product.</p> <p>'Performance' is defined as 'the action of a medical device in performing its intended function'. The phrase 'process performance' does not correlate with this definition.</p> <p>Proposed change:</p> <p>Review and ensure consistency.</p>	
258	L158	14, 31	<p>Comment: "Non-integral DDCs should be CE marked in accordance with the MDR."</p> <p>This statement does not allow for flexibility to reference devices CE marked to MDD with a valid EC certificate beyond 26 May 2020. It is unclear if the intention of the first sentence, "Non-integral DDCs should be CE marked in accordance with the MDR." was to state that only the device is to be CE-marked?</p> <p>Proposed change (If any): Medical devices CE marked to MDD will still be allowed on the EU market for a time-limited period in accordance with MDR if the EC certificate is valid. This period of validity for a device's CE mark should also apply in the context of non-integral DDCs. Change text to: The medical device of a non-integral DDC should be CE marked...</p>	The comment is acknowledged. Reference is made to the updated Q&A (June 2021) on the MDR implementation.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
259	L158	14	<p>Comment: Clarification in relation to non-integral DDCs and the requirement and applicability of the MDR to the medical device is needed. Rewording of the paragraph is proposed as follows, to aid interpretation and avoid any misunderstanding.</p> <p>Proposed Change (if any): The 1st sentence should be revised to read as follows:</p> <p>“For non-integral DDCs, the medical device must be CE marked in accordance with the MDR¹. The conformity assessment should be appropriate for the classification of medical device and involve an appropriately-designated Notified Body where appropriate to do so. Inclusion of a NBOP in lieu of an EU Certificate of Conformity (or EU Declaration of Conformity issued by the device manufacturer) is not appropriate if that device can be used separately as a medical device and meets the definition of Article 1 (2).</p> <p>Where a CE marked device for the administration of the medicinal product is co-packaged or is referred to in the SmPC of a marketing authorisation, additional information may need to be provided by the applicant with regards to the device if the device may have an impact on the quality, safety and/or efficacy of the medicinal product.</p> <p>¹Medical devices CE marked against the MDD will still be allowed on the EU market for the time-limited period as set out in Art 120 of MDR, if the EC certificate is valid.”</p>	<p>The comment is acknowledged, however the text has been retained. Regarding the footnote, the guideline relates only to the Medical Device Regulation and is not considered applicable for the Medical Device Directive. No change to the guideline is proposed.</p> <p>Reference is also made to the updated Q&A (June 2021) on the MDR implementation.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
260	L158	19	<p>Comment: The statement that non-integral DDCs should be CE-marked is incorrect and will cause confusion across industry. The device provided in a non-integral DDC shall be CE-marked, but not the overall product.</p> <p>Proposed change: Correct the text.</p>	The comment is acknowledged, and the guideline has been amended to refer to the medical device component of the non-integral DDC.
261	L158	21	<p>Comment: To add a proposed indication</p> <p>Proposed change (if any): Non-integral DDCs should be CE marked in accordance with the MDR, while integral DDCs should not be CE marked.</p>	The comment is acknowledged, however, this is already considered clear in the guideline and no further update is proposed.
262	L159	23	EMA must not accept this situation. Any medicinal product that must be measured and/or administered should be accompanied by an appropriate, sufficiently accurate dosing device that has been assessed for quality and clinical safety and efficacy, and has undergone user testing by a target patient group and/or health professionals.	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
263	L159-161	18	<p>Comment: Refer to cross labelled</p> <p>Proposed change (if any):</p> <p><i>Non-integral DDCs should be CE-marked in accordance with the MDR. Where a CE-marked device for the administration of the medicinal product is co-packaged or is referred to in the SmPC of a marketing authorisation (cross-labelled), additional information may need to be provided by the applicant with regards to the device, if the device may have an impact on the quality, safety and/or efficacy of the medicinal product.</i></p>	The comment is acknowledged however this terminology is not used in the MDR, therefore no update to the guideline is proposed.
264	L160	14	<p>Comment: In the context of non-integral, co-packaged, DDCs cross referred in SmPC 'additional information may need to be provided by the applicant': how will this work if the applicant has no direct relationship with the supplier? Could applicant be expected to perform additional clinical studies? Who would own the data or any label claim?</p> <p>Proposed change (if any): Clarify: expectation is presumably that the medicinal product-specific risk is addressed. Applicant is accountable but should be able to work with device supplier to provide additional information, e.g. device supplier should be able to file relevant info on behalf of the applicant.</p>	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
265	L160-161	14	<p>Comment: This text suggests that only if the device may have an impact on quality/safety/efficacy of the medicinal product, then additional information may need to be provided for the device, in the case of a non-integral DDC.</p> <p>In other words, if the device will not have an impact, then no information for the device needs to be provided. However, the requirements listed through the entire Chapter 6 of this guidance contradicts the latter interpretation.</p> <p>Therefore, it is recommended to clarify the sentence "... additional information may need to be provided by the application with regards to the device if the device may have an impact on the quality, safety and/or efficacy of the medicinal product".</p>	The comment is acknowledged the text has been modified
266	L161	14	<p>Comment: It is unclear how the device potentially having an impact on the quality, safety or efficacy of the Medicinal Product will be established, specifically in this case where no further information has been provided. It should be explained how the medicines CA will make this judgement; or whether the Applicant should provide justification that this is not the case.</p> <p>Proposed change (if any): ... if the device may have an impact on the quality, safety and/or efficacy of the medicinal product as described in the justification of P2.6.</p>	The comment is acknowledged the text has been modified

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
267	L161	19	<p>Comment: It is unclear how the device potentially having an impact on the quality, safety or efficacy of the Medicinal Product will be established, specifically in this case where no further information has been provided.</p> <p>Proposed change (if any): It should be explained how the medicines CA will make this judgement; or whether the Applicant should provide justification that this is not the case.</p>	The comment is acknowledged the text has been modified
268	L162	3	<p>Comment: In these lines it is recommended to seek the opinion from a <i>medical device CA</i> in case of doubt as to the proposed classification according to the MDR, where – for medical devices – it should be the Notified Body (NB). On the other hand, ultimate decision for classification is with the medical device competent authority (CA):</p> <p>See Art 51:</p> <p>Any dispute between the manufacturer and the notified body concerned, arising from the application of Annex VIII, shall be referred for a decision to the competent authority of the Member State in which the manufacturer has its registered place of business.</p> <p>Proposed change (if any): Please clarify</p>	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
269	L162	35	It is not clear the recommendation of asking the medical device CA an opinion on the classification. Is the Notified Body the most appropriate Body for releasing an opinion, being also the Body to performs the conformity assessment? Many Notified Bodies allows Manufacturers to interact and ask a preliminary opinion on the documentation (a sort of medical device scientific advice) before applying for the CE mark request. During these meetings it is possible to require an opinion on the medical device classification.	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
270	L162-163	8	<p>The draft guideline states: <i>"In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA."</i></p> <p>We recommend to clarify which authority shall be contacted:</p> <ul style="list-style-type: none"> - The authority of the member state where the medical device manufacturer is established - The authority of the member state where the medical NB is established - The authority of the member state where the medical applicant (future MAH) is established - And the topic becomes even more difficult for users of the centralised procedure: is an advice of a national competent authority sufficient or is it possible for the applicant to contact the Medical Device Coordination Group (MDCG) as established acc. Article 103 (MDR) and in accordance with its duties referred to in Article 105 (MDR) letters "f" and "h"? Or will there be an option to channel the request through the EMA Innovation Office? 	<p>The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
271	L162-163	10	<p>Comment:</p> <p>Not all co-packaged products will meet the criteria of the DDC guideline, for example in the case of products for reconstitution. It is suggested to indicate that EMA may be consulted where there is any doubt.</p> <p>Proposed change:</p> <p>In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA. In cases of doubt as to whether a co-packaged product is classified as a drug device combination product for regulatory purposes, it is recommended that an opinion be sought from EMA.</p>	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.
272	L162-163	14	<p>Comment: Generally, this works if a company has a manufacturing presence in EU. Given that many companies outside the EU rely on other "Economic Operators" (as defined in MDR 2017/745), we suggest to amend the text as follows.</p> <p>Proposed change (if any): In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA, or in consultation with Notified Body and/or Authorized Representative, if appropriate.</p>	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.
273	L162-163	18	<p>Comment: This sentence does not appear to be relevant for a Guideline for Marketing Authorisation Applicants and does not impact on the quality requirements for a DDC, especially</p>	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>given the statement regarding the Guideline intent in sentence 164-166</p> <p>Proposed change (if any):</p> <p>Remove sentence:</p> <p>In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA.</p>	
274	L163	14	<p>Comment: To reduce the burden of questions relating to proposed classification to the CAs would it not be more convenient to seek the opinion of either the Competent Authority (CA) or a Notified Body?</p> <p>Proposed change (if any): Opinion to be sought from a medical device CA or a Notified Body.</p>	The comment is acknowledged, and the guideline has been amended accordingly. Reference to classification is outside the scope of the guideline.
275	L163	14	<p>Comment: It may be prudent to include the three cumulative conditions for Integral DDCs which is stated in the EMA Q&A document.</p> <p>Proposed change (if any):</p> <p>A single integral DDC product means:</p> <p>The following three conditions are met at the point of placing on the market:</p> <ul style="list-style-type: none"> • the device and medicinal product form a single integral product; • intended exclusively for use in the given combination; 	The comment is acknowledged. The definition of single integral DDC is already included in the introduction and no change is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> • which is not reusable 	
276	L163	5	What is a medical device CA? Don't all national CA's have responsibility for devices?	The comment is acknowledged. The NCA of each member state will differ with respect to division of responsibilities. However, classification is outside the scope of the guideline and text has been revised.
277	L163	17	<p>Comment: Given that Sponsors may not be familiar with the term "medical device CA", we recommend that the Agency clarify that a medical device CA in a given country may be a separate entity from the national CA.</p> <p>Proposed change (if any):</p> <p>"In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA, which may be a separate entity from a member state's national CA."</p>	The comment is acknowledged. The NCA of each member state will differ with respect to division of responsibilities. However, classification is outside the scope of the guideline and text has been revised.
278	L164	14	<p>Comment: Clarification that guideline referenced is the current document.</p> <p>Proposed change (if any): The requirements laid down in the this guideline relate to the quality of the DDC,</p>	The comment is acknowledged and the guideline has been amended accordingly.
279	L166-167	14	<p>Comment: This paragraph states that the requirements laid down in the guideline relate to the quality of the DDC, including the manufacturing and control methods thereof. It also acknowledges that specific information may be required to fulfil the requirements of other EU guidances (e.g. ICH guideline M7). Although the requirements are not clearly stated, it appears that they refer to the ICH guidelines</p>	The comment is acknowledged. Additional text has been included for clarification.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>relevant to impurities, e.g. ICH M7 on DNA reactive (mutagenic) impurities. Additional clarification regarding interface of the EU GMP requirements for Device related technical files expectations from the notified bodies would be appreciated.</p> <p>Proposed change (if any): Please consider replacing the last sentence with: "It is however, acknowledged that specific information may be required to fulfil the requirements of other EU guidance (e.g. ICH guideline M7) important to consider relevant ICH and EU guidance on genotoxic and non-genotoxic impurities including, but not limited to, ICH Q3A, Q3B, Q3C, Q3D and M7.</p> <p>Obligations from the EU GMP guide should also be adequately followed".</p>	
280	L168	14	<p>Comment: Samples of the DDC should be provided on request.</p> <p>Proposed change (if any): Recommend adding clarification on who, when and why samples of the DDC be provided.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised</p>
281	L168	3	<p>Comment:</p> <p>It is kindly requested to add information as to the intent of requesting samples. This request is mainly in order to understand the number of required samples and specific finishing (like attached labels), and to understand under which typical circumstances samples would be requested.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>
282	L168	9	<p>Please clarify at which point during the MAA review that samples may be requested.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
283	L168	19	<p>Comment: The request for samples should be explained further. Are samples expected to be for human use, within expiry date, drug-filled etc? Are samples expected to be in full secondary packaging and carrying all associated information, label etc? Are representative 'safe' samples adequate? What supporting documentation should be provided with samples, if any? How will disposal or return be managed?</p> <p>Proposed change: Clarify the overall expectations here.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>
284	L168	24	<p><i>Quote</i></p> <p>Samples of the DDC should be provided on request.</p> <p>Comment/ Proposed change</p> <p>Please clarify if this is an additional requirement or refers to the already defined requirements (e.g. CMDh/260/2012, Rev.6).</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>
285	L168	35	<p>It has to be clarified to who and when samples of the DDC should be provided.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>
<u>4.1. GENERAL CONSIDERATIONS – APPLICATION OF STANDARDS (L169-171)</u>				
286	L169	19	<p>Comment: It is not clear whether EMA intend the reference to 'ISO standards' to apply to process standards such as ISO 13485, ISO 15378, ISO 14971, etc; or to technical standards such as ISO 11608, ISO 20072, etc.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): Clarify the type of standards.	
287	L169	19	<p>Comment: The position with respect to precedence needs further thought.</p> <p>Firstly, the use of normative standards is commonplace in Industry and the expectation of Notified Bodies to develop, test and assess device constituents, confirming state of the art. Notified Bodies are unlikely to be able to immediately assess device-related information presented against pharmaceutical testing requirements.</p> <p>Secondly, if Industry Applicants are to be expected to test device constituents against the established and recognised normative standards, and test the DDC only against the Ph.Eur/monographs, this may create duplicate effort (and potentially conflicting results) – due to different sampling requirements, statistical analysis and methods.</p> <p>Thirdly, there are some specific examples where Ph.Eur/monograph and normative standard requirements do not align. Several Ph. Eur/monograph tests start from the assumption of homogenous batch manufacture and therefore allow low numbers of test samples to be taken. Device manufacturing is often not as homogenous, carrying variability from several sources. Although all devices may be manufactured to a specification, that specification is often wide in some respects and there is some degree of variability in manufactured items. As such, larger quantities of test samples should typically be taken.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Fourthly, neither monographs nor normative standards take account of the risk profile of the product. The expectation is that the Applicant considers the applicability and the rigour of the described requirements and adapts this as appropriate. There are cases where the risk justifies an expanded number of test samples, tighter acceptance criteria or even different test methods to those proposed in established monographs or standards.</p> <p>Proposed change (if any): The text could be made more flexible as so; For DDCs that are designated as Medicinal Products, Applicants are expected to fulfil regulatory requirements for Medicinal Products. This includes testing against the prescribed Ph.Eur chapters or monograph(s). In cases where such tests require adaptation to the risk profile of the product; or where established and recognised normative standards describe a more appropriate approach, these may be used as an alternative. In such cases, justification should be provided.</p>	
288	L169	19	<p>Comment: The term 'ISO standards' is used here very specifically and excludes many other types of normative standards.</p> <p>Proposed change (if any): Adjust to 'normative standards' or some other more expanded term.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
289	L169-171	3	<p>Comment: When demonstrating fulfilment of GSPRs for a medical device, compliance with standards (e.g. ISO, IEC, ASTM ...), is used. Specifically, when fulfilling harmonized standards compliance with GSPRs is presumed. A justification for use of alternative standards is required. For aspects related to devices, ISO and other technical standards should be considered to be equivalent to Ph. Eur. and ICH guidelines. This reflects also NB expectations during conformity assessment / assessment of fulfilment of GSPRs.</p> <p>Proposed change (if any):</p> <p>Reword second sentence to read "For medical device aspects" ISO standards and other technical standards are equivalent to Ph. Eur. requirements and European and ICH guidance.</p>	The comment is acknowledged and the guideline has been modified.
290	L169-171	14	<p><u>HIGH PRIORITY</u></p> <p><u>Comment:</u> Applicability of Standards. Clarity requested on the scope of applicability. Does this applicability apply to technical requirements and quality system requirements? e.g. For GSPRs, European and ICH requirements take precedence? The ISO standards are typically focused only on the device and if the ICH guidelines are not specific enough to cover the performance and safety aspects of the device, this approach could result in safety and quality problems with the device.</p> <p>The sentence should likely use the term "international standards" since ISO is only one of many international standards publishers.</p>	<p>The comment is acknowledged.</p> <p>The wording in the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): As compliance to both relevant parts of Ph. Eur. and ISO standards are required, it is suggested to either delete line 171 or rephrase – Ph.Eur. requirements and European and ICH guidance-take precedence over ISO and other international standards.	
291	L170	10	<p>Comment:</p> <p>Application of standards should be limited to the drug product part.</p> <p>Proposed change:</p> <p>Suggest adding the following: Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated.</p> <p>Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards as far as the drug-product part is concerned.</p>	The comment is acknowledged, the wording in the guideline has been revised.
292	L170-171	6	It is stated that Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards. It is not clear how this can be achieved when the opinion / CE-marking of the Notified Body of GRSPs will be based on ISO standards.	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
293	L170-171	9	<p><u>Comment – CRITICAL – NEED TO CLARIFY; PROVIDE SPECIFIC EXAMPLES</u></p> <p>The change proposed below aims to clarify the quality requirements leading the development of the two constituents of a DDC (drug product and device). If the development of the device constituent is considered, Ph. Eur. chapter(s) or monograph(s) and ICH guidance cannot take precedence over ISO standards.</p> <p><u>Proposed Changed Text</u></p> <p><i>Compliance of the drug component of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards as far as the requirements for the drug component of a DDC are concerned.</i></p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.
294	L170-171	11	<p>Comment: Compliance of a DDC with relevant Ph. Eur. Chapter(s) or monograph(s) should be demonstrated. Ph. Eur. Requirements and European and ICH guidance take precedence over ISO standards.</p> <p>Proposed change (if any): Add to this sentence: In the event that a specific attribute is not covered by Ph. Eur. Requirements and European and ICH guidance, ISO standards shall apply especially if part of the list of Harmonized standards</p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
295	L170-171	16	<p>Comment: Guidance document state 'take precedence over ISO standards'. Within the field of Medical Devices there are ISO, IEC and ETSI standards that can be applicable to Medical Devices. If these standards are harmonised this indicate a strong recommendation to use these standards as a tool to show compliance and the text in 171 may not be accurate.</p> <p>Proposed change (if any): Propose EMA to have discussions with Medical Device Regulators for harmonised view and wording.</p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.
296	L170	5	<p>Related to applicability of standards, it is outlined that "Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. <u>Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.</u>"</p> <p>In terms of the NBOp which considers the assessment of Annex I of the MDR, the applicability of harmonised standards and upcoming common specifications are taking precedence over European and ICH guidance for medicinal substances.</p> <p>Within the MDR, the focus is set on harmonised standards, common specifications as well as state of the art (see as (22) and (23), Article 1,2. as well as Article 8,1. of the MDR).</p> <p>Thus, clarification on this statement is needed; it has to reflect the medical device related regulatory requirements as well.</p> <p>Proposed change (if any):</p> <p>Related to applicability of standards, it is outlined that "Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. <u>Ph.Eur. requirements</u></p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p><u>and European and ICH guidance take precedence over ISO standards for the medicinal product.</u>” For the medical device, harmonised standards, common specifications as well as state of the art take equivalent level of consideration to Ph.Eur and European and ICH guidance.</p> <p>The wording “ICH guidance take precedence over ISO standards” should be deleted as for the device part ISO standards and harmonised standards could be more relevant and may include additional requirements.</p>	
297	L171	8	Will the Ph. Eur. Requirements as well as the European and ICH guidance and their interpretation by the Competent Authorities as well bind the power of the Notified Bodies, where they would favour the ISO standards?	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.
298	L171	19	<p>Comment: Precedence should perhaps be only applied when there are direct comparisons or conflict.</p> <p>Proposed change:</p> <p>‘...take precedence over normative standards in case of conflict.’</p>	The comment is acknowledged. The wording has been revised

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
299	L171	24	<p><i>Comment</i></p> <p>As far as the medical device part is concerned, according to Art. 8 MDR it is state-of-the-art to provide evidence for devices following the relevant Harmonised ISO Standards. Ph. Eur. requirements should be preferred depending on the indication and administration of the medicinal product and for safety reasons only.</p> <p>Proposed change</p> <p>Ph. Eur. Requirements and European and ICH guidance take precedence over Harmonised ISO Standards as far as the medicinal product is concerned.</p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.
300	L171	25, 31	<p>Comment: Harmonized standards vs Ph Eur and ICH. It is unclear why the standards (e.g. ISO 11608 series) would not have adequate requirements.</p> <p>The use of Ph. Eur. requirements and European and ICH guidance should not by default take precedence over ISO standards or common specifications. Compliance should be based on suitability. Compliance with harmonised standards and common specifications could be a prerequisite for ensuring compliance with GSPRs. Under MDR article 8.2 ISO standards and Ph. Eur. requirements are considered equal.</p> <p>Proposed change (if any): Delete line 171</p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
301	L171	28	<p>Comment:</p> <p>Statement regarding Ph. Eur and European and ICH Guidelines is definitive. It indicates that compliance with those requirements ALWAYS take precedence, even if a more precise standard exist.</p> <p>An example would be requirements of Coring and Resealability of a (pen) cartridge closure. In that case ISO11608-3 protects the patient by requiring a barrier that is more relevant for the expected exposures.</p> <p>Proposed change (if any): Delete line 171</p> <p>or</p> <p>Edit to read:</p> <p>Ph. Eur. Requirements, European and ICH guidelines applies; however, international standards may be considered if those standards are more precise in its requirements in the particular application.</p>	The comment is acknowledged. This wording refers to the assessment of the CA, which includes review of the NB opinion.
<p><u>4.2. GENERAL CONSIDERATIONS – SUBMISSION OF DATA, ITS LOCATION IN THE DOSSIER AND ITS FORMAT</u></p> <p><u>(L172-189)</u></p>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
302	L173-175	18	<p>Comment: While it is appreciated that this Guideline very much sets out the expectations for inclusion of device information within the eCTD for CA oversight, it would be beneficial to include a statement pointing to the NB expectations and documentation required to verify the GSPRs are met, shall differ within this section.</p> <p>Proposed Change (if any):</p> <p><i>To facilitate the CA assessment, information on the device should be provided in a clearly structured manner, following the electronic Common Technical Document (eCTD) format (Volume 2B Notice to Applicants Medicinal Products for Human Use – Presentation and Format of the Dossier). The technical documentation requirements to satisfy the NB review and opinion are outside of the scope of this Guideline and discussion with the NB to confirm their expectations should be undertaken.</i></p>	The comment is acknowledged. The guideline discusses CA assessment. The requirements of the NB are out of scope of this guideline.
303	L178-182 and L405	14, 19	<p>Comment: Clarification requested if all requirements of Annex I of MDR are applicable (for example regarding labelling); propose further clarity/reference to relevant document should be added and for accuracy, this text should refer to the relevant GSPRs.</p> <p>Proposed change (if any): add relevant</p>	The comment is acknowledged, the text has been modified.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
304	L178-180	14	<p>Comment: Provide clarification that in cases involving a filled integral DDC, it is sufficient to provide evidence of conformity to MDR Annex I (e.g., a NB Certificate of Conformity) for the empty device component, along with the product-specific quality aspects related to the device for the filled DDC provided in Module 3.2.P as described in this guidance.</p> <p>Proposed change (if any): With regards to the structure of Module 3, Section 3.2.P should contain quality information on the product-specific quality aspects related to the device component of the medicinal product relevant to which impact the quality, safety and efficacy of the medicinal product.</p>	The comment is acknowledged, and the guideline modified for clarification.
305	L178-180	24	<p><i>Comment</i></p> <p>CTD section 3.2.P does not deal with safety nor efficacy</p> <p><i>Proposed change</i></p> <p>“With regards to the structure of Module 3, Section 3.2.P should contain information on the product-specific quality aspects related to the device relevant to the quality, safety and efficacy of the medicinal product.”</p>	The comment is acknowledged; the text has been modified

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
306	L178-182	23	The following information should be provided: dose per graduation unit; the standard deviation of measured values; unit of measurement of the graduation scale (mg or mL); minimum and maximum values; numbered and unnumbered increments on the graduation scale. The marketing authorisation applicant should explain and justify these choices. They should be validated by the drug regulatory agency concerned. Their evaluation should be documented in a "Usability and Packaging" section of the EPAR.	The comment is acknowledged; however, this is outside the scope of this guideline.
307	L181 and L405	14, 19	Comment: MDR Annexes are numbered in roman numerals. Proposed change (if any): Change 'Annex 1' to 'Annex I'.	The comment is acknowledged, and the text modified.
308	L181	9	Comment Should align with options presented in 5.4.2.a (line 409) Proposed Changed Text <i>Section 3.2.R should include relevant information related to the demonstration of compliance of the device(s) with MDR Annex 1 (the GSPRs) e.g. NBOP, NB Certificate of Conformity and/or device manufacturer's EU Declaration of Conformity or Applicants confirmation</i>	The comment is acknowledged, reference has been made to the relevant section of the guideline for further information.
309	L183-187 and L571-572	31	Comment: In the lines 183 -184 it is stated that "[...] Module 3 should include appropriate information on the [.....] usability of the DCC [...].	The comment is acknowledged and the wording has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>In the lines 184 - 187, it is said that "[...] usability and human factor studies [.....] could be included in section 5.3.5.4 [...], with appropriate reference to Module 3 [.....].</p> <p>In the lines 571 – 572 it is stated that "Detailed information on usability [...] should be presented in Module 5. A summary should be provided in Module 3.2.R, cross-referring to Module 5."</p> <p>These instructions are not consistent ("Module 3, Module 3.2.R, Module 5, section 5.3.5.4") and therefore rather confusing. It should be consistently clear what kind (or: level) of information on usability is expected in which section of the dossier, and to which section reference should be made. Over-all, we would not expect Module 3 to include detailed or extensive information on usability. However, the wording of the Guideline should be consistent.</p> <p>Proposed change:</p> <p>Line 183: In general, Module 3.2.R of the MAA dossier should include [.....]</p> <p>Line 184 – 185: Detailed usability und human factor studies [...] should be included in section 5.3.5.4, [...] with appropriate reference to Module 3.2.R [...]</p> <p>Line 572: "[...] be presented in section 5.3.5.4. A summary [...] cross referring to section 5.3.5.4.</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
310	L184	3	<p>Comment: It is not clear if the human factors and usability studies will be assessed by the Competent Authorities and/or the Notified Body, respectively. Double assessment will lead to ambiguities and should be avoided.</p> <p>Proposed change (if any): Provision of more detailed information about responsibilities of the Competent Authorities and Notified Body for assessment of human factors and usability studies and if assessment made by one party could be recognised by the other party.</p>	The comment is acknowledged; however, this is outside the scope of this guideline.
311	L184	19	<p>Comment: It may be beneficial to separate usability of the device constituent from usability of the combined product – especially when discussing co-packed products. This may also help with clarifying to industry that usability of the product remains a review point for the medicines Competent Authority, whilst usability of the device/device constituent remains a Notified Body topic.</p> <p>Proposed change: Provide explanation of these two different concepts at an appropriate place in the guideline.</p>	The comment is acknowledged; however, no change is proposed as this is clarified in the core precept of the guideline (section 4).
312	L184	25, 28	<p>Phrasing indicates a particular format for Usability and human factor studies for DDC's.</p> <p>Proposed change (if any): Add: Information on manufacture, control and usability of a non-Integral DDC can be supplied in any suitable format chosen by the manufacturer.</p>	The comment is acknowledged; however, no change to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
313	L184-187	19	<p>Comment: Typically, Human Factors data is not clinical data. Simulated use has become common practice for the execution of Summative/Design Validation HF studies and such data gathering is often conducted in non-clinical settings. Actual-use studies are only performed in very specific situations. HF studies are not weighted similarly to clinical studies. It is therefore recommended to NOT confuse HF studies with Clinical Studies and to NOT place HF study data in Module 5. This position is normally adopted with submissions to US-FDA (despite conflicting guidance) and it would be beneficial to industry to drive for harmonisation in this respect.</p> <p>Proposed change (if any): Suggest that HF data be included in Module 3.2.R. If the HF data does carry any clinical relevance, then a reference to the information can be added into Module 5.</p>	The comment is acknowledged; the wording in Section 5.4 of the guideline provides additional guidance. No further change is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
314	L184-186	14	<p>High Priority</p> <p>Comment: Whilst it appears to be only a suggestion, usability and human factors (HF) are in almost all cases not clinical studies, and so would sit better in Module 3. Referencing of usability & HF data in M5 (5.3.5.4.) should further be optional as HF data is NOT clinical data and is collected from simulated use studies. The draft guideline notes that human factor studies <u>could</u> be included in section 5.3.5.4, 'Other Clinical Study Reports' of the CTD. It would be appreciated if guidance on alternative CTD sections for inclusion of human factors could also be provided.</p> <p>Proposed change (if any): Either delete sentence OR Suggest that HF data be included in Module 3.</p> <p>If the HF data does carry any clinical relevance, then a reference to the information can be added into Module 5.</p> <p>"Where clinical studies are used to obtain usability data, they could be included in section 5.3.5.4, 'Other Clinical Study Reports' of the CTD, with appropriate reference to Module 3 as these may be reviewed".</p>	The comment is acknowledged; the wording in Section 5.4 of the guideline provides additional guidance. No further change is proposed.
315	L184-186	31	<p>Comment:</p> <p>"Usability and human factor studies are multidisciplinary in nature and could be included in section 5.3.5.4, 'Other Clinical Study reports' of the CTD, with appropriate reference to Module 3..."</p> <p>Proposed change:</p>	The comment is acknowledged; the wording in Section 5.4 of the guideline provides additional guidance. No further change is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Recommend including usability and human factor studies in Module 3.</p> <p>Usability and human factor studies are not clinical studies, so the more appropriate location for this information seems Module 3. Typically, these studies are simulated use studies with no patient administration or treatment and are performed to validate the design and performance (i.e., quality attributes). Alternately, suggest this information may be provided in Module 3 and cross-referenced in Module 5 to Module 3.</p>	
316	L184-187	14	<p>Comment: Clarification if Usability and Human Factor studies will be reviewed by Notified Body and CA? This is already part of Annex I and therefore the opinion of the NB. Potential for confusion?</p>	The comment is acknowledged. No change to the guideline is proposed; the assessment by CA and NB is explained in the core precept of the guideline (Section 4).
317	L184-187	24	<p><i>Comment</i></p> <p>Usability and human factor studies are multidisciplinary in nature and could be included in section 5.3.5.4, 'Other Clinical Study Reports' of the CTD, with appropriate reference to Module 3 as these may be reviewed by both pharmaceutical and clinical assessors, each with different focus.</p> <p>CTD Module 3 does not deal with pharmaceutical and clinical aspects. Moreover, it is common practice in national competent authorities that the respective assessor only has access to the relevant section for his evaluation and not the complete CTD. Hence, a presentation of the documentation in a section, which is normally not in focus of the assessor, might be overseen.</p>	The comment is acknowledged; however, this is outside the scope of this guideline and no change is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
318	L184 and L185	14	<p>Comment: ".....could be included in section 5.3.5.4, ..."</p> <p>Proposed change (if any): It should be clarified whether usability and human factor studies are required to be included. If the device is properly CE marked, then it seems redundant to be included. If the device is integral, then data should probably be included unless otherwise justified.</p>	The comment is acknowledged, and reference is made to Section 5.4 of the guideline.
319	L184 and L446	14	<p>Comment: Refers to "patient" populations, but DDCs can also be used by healthcare professionals or lay caregivers, not only by patients themselves.</p> <p>Proposed change (if any): Talk of "users" instead (throughout the document) and define users as patients (including healthy subjects such as vaccine recipients), lay caregivers, or healthcare professionals.</p>	The comment is acknowledged, and the guideline has been reviewed to ensure consistency of terminology.
320	L185	6	<p>'could' is too vague with respect to a location were data have to be presented</p> <p>Proposed change (if any):</p> <p>'should'</p>	The comment is acknowledged, and reference is made to Section 5.4 of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
321	L185	10	<p>Comment:</p> <p>We disagree that the usability and human factor studies should be provided in eCTD M5. They are not considered as clinical investigational studies, and rather to ensure that the product can be operated safely and effective by the intended user. A human factor engineering report will summarize the formative human factor study results and the final summative human factor study results. This is standard practice in an US NDA/BLA. In addition, it is in line with the eCTD specification for ICH.</p> <p>Proposed change:</p> <p>Suggest to provide the human factor engineering report in 3.2.R without the need of a summary of the report.</p>	The comment is acknowledged, and reference is made to Section 5.4 of the guideline.
322	L186 L291 L445	14	<p>Comment: Replace all instances of the term "Human Factor" with the term "Human Factors" throughout the document to more accurately reflect the discipline name.</p>	The comment is acknowledged, and the guideline has been reviewed to ensure consistency of terminology.
323	L188-189	14	<p>Comment: Please could the agency clarify what is meant by "combined ATMP" in comparison to "ATMP"?</p> <p>ATMPs were excluded from this guidance. Why mentioned here? (see line 114: "Article 117 of the MDR does not apply to ATMPs.")</p> <p>Proposed change (if any): Clarification regarding ATMP needed or ATMP references to be removed from guidance.</p>	<p>The term combined ATMP is defined in Article 2(1)(d) of Regulation (EC) No 1394/2007.</p> <p>The text has been revised to clarify the reason for mention of ATMPs</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
324	L188-189	18	<p>Comment: As combined ATMPs are outside of the scope of this Guideline it is not clear why this sentence has been included</p> <p>Proposed change (if any):</p> <p>Remove sentence</p> <p>For ATMPs, the content of the MAA may be adapted, provided that this is justified under a risk-based approach.</p>	The text has been revised to clarify the reason for mention of ATMPs
<u>4.3. GENERAL CONSIDERATIONS – PLATFORM TECHNOLOGY/TECHNOLOGIES (L190-198)</u>				
325	L190	2	<p>Comment:</p> <p>“Platform technologies”</p> <p>Correct use of inhalers can be complicated and can be illustrated by some examples from just one of our primary care members’ clinical practice: one patient was putting a strip of Rolenium in the opposite way as this wasn’t mentioned in the information. Another patient swallowed the capsule that was intended to be used in the inhaler as he couldn’t imagine that a capsule could be used in another way (e.g. in an inhaler). Another patient didn’t remove the cap of the inhaler. One that thought he should lay in the floor to take the inhalation.</p> <p>Proposed change (if any):</p> <p>Take into consideration health literacy and cultural issues.</p> <p>Instructions should be as simple as possible with photos and videos to support. Readable and applicable to a child.</p>	The comment is acknowledged; however, this is outside the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Drawings or other visual representations of the correct use of inhalers can also be helpful.</p>	
326	L190	5	<p>This line identifies platform technology/ technologies. Would EMA/ CA accept a "Device Master File"- like solution for platform technologies? A first NB review of a platform without considering the impact of a certain medicinal product on the device part will be performed once as a so-called "pre-NBop".</p> <p>In addition, a second review will be performed for each customization during NBop (e.g. focus on maintenance of GSPR's, impact of drug characteristics on the delivery system and usability). Potentially this could mean that multiple NB's will be involved to both cover the "DMF" Platform file and the customized version.</p> <p>Background Information: A similar system is used at the FDA. There is no legal framework within the EU. The MDR does not outline such an approach.</p> <p>This would require "mutual recognition "of NBop's.</p>	<p>The comment is acknowledged. The device master file concept is not currently foreseen in the EU legislation.</p> <p>Mutual recognition of NBops is a matter outside EMA remit.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
327	L190	19	<p>Comment:</p> <p>Use of the term 'platform' requires elaboration.</p> <p>The definition in Section 10 only extends to technologies that have previously been approved for another medicinal product. This effectively excludes MANY co-packed CE-marked devices, since these are rarely approved only for a specific medicinal product.</p> <p>Distinction probably needs to be made between device-developer/device-supplier technology platforms, and 'internal' multi-use platforms established by Applicants. For example, a pre-fillable syringe developed and specified by a device developer/supplier may need to be handled differently to a pre-fillable syringe platform used by a PharmaCo for several molecules in their pipeline. The former may be sold and distributed widely for many intended uses whilst the latter may be customised for the PharmaCo for use in a specific user group.</p> <p>The responsibility; management of change; understanding of interactions with the drug constituent; understanding of risk; documentation; and data, are all potentially different between the two scenarios.</p> <p>Furthermore, a device-supplier technology could not be a platform (by the definition in section 10) until one client has had it approved with their medicinal product. This model may cause confidentiality and exclusivity issues.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any): Consider EMA expectations for the kind of 'discussion' and 'justification' needed from the Applicant in these two different cases of platforms.</p> <p>For example, how should post-approval changes to a device-supplier platform be handled? The device-supplier will not have made the original MAA submission and therefore cannot make a Variation. Multiple submissions are likely to have been made (potentially across multiple CAs) by the PharmaCo Applicants leveraging the technology. They would potentially all have to submit a Variation when notified by the device-supplier. However, the device-supplier may have obtained a single NB Opinion independently of the PharmaCo Applicants. Should the device-supplier therefore raise the change with the involved Notified Body? Or with the Competent Authority/ies?</p> <p>How should this be handled if the PharmaCo sought the Notified Body Opinion based on the device-supplier platform?</p>	
328	L190	28	<p>Comment:</p> <p>Intension is not clear; in particular, when medical device component development is outsourced.</p> <p>Maybe the section can be split in two cases:</p> <p>Case a) Applicant owns the platform and</p> <p>Case b) Applicant buy (supplier control) technology</p> <p>Proposed change (if any): Add:</p> <p>For platform technology/technologies owned and controlled by applicant please use Annex 2.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			If applicant has an agreement with supplier of technology platform the applicant can include a NBOp provided to the applicant by an approved supplier	
329	L190	28	<p>Comment:</p> <p>Risk analysis is part of GSPR's and will often depend on the drug administered – Unless the drugs have identical risk profiles it is feared that use of the platform technologies concept could raise more confusion than clarity.</p> <p>Proposed change (if any):</p> <p>Consider describing the split between the assessment of a generic NBOp for a platform and the drug specific aspects being added in the MAA without review of a NB as this helps to avoid conflicts due to different assessments by various NBs on a technically generic platform.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.
330	L190-198	10	We do appreciate that Annex 2 of the guideline provides the option of including a 'Letter of Authorisation' from the technology owner. We encourage EMA to provide additional details such as 1) examples of platform technologies (e.g. commercially available syringe/pen/auto-injector 2) what documentation would be required for the 'platform technology part (e.g. declaration of conformity) and 3) what specific data are to be provided pertaining to the DDC including suitability to the target patient population.	The comment is acknowledged, the text has been modified and no longer mention platform technology.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
331	L190-198	14	<p>Comment:</p> <p>A platform device may cover a range of product realisations, it is not clear where the attributes specific to the individual device are described: in the documentation to the NB and the NB report or in the MAA or in both.</p> <p>If changes to the existing platform device are made, it is not clear if this will trigger an exchange of the "letter of authorization", a new Notified Body opinion and/or a variation to the competent authority.</p> <p>If adaptations to the device within a platform are realized, it is not clear if it is sufficient that this is evaluated under responsibility of the MAH or if a variation/notification to the CA and/or to the NB necessary. Examples of data to be included for a platform device would be helpful.</p> <p>Proposed change (if any):A summary of the (relevant) data for those aspects of the device which pertain to the 'platform' should be presented in the relevant sections in Module 3.2.P (e.g. for an administration device comprising at least route of administration, mode of action, intended use for which the platform has previously been reviewed by a Notified Body, critical product attributes as far as part of the release specification of the DDC; these should be clearly indicated in relevant sections of Module 3.2.P and should include options of references to detailed information presented in 3.2.R (e.g. the letter of authorization as referred to in Annex 2 of this document). Suitability with regards to specific medicinal products and subsets of the target patient population should be demonstrated.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Reference to previously approved DDC(s) developed and marketed by the marketing authorization holder (MAH) may be included as supportive information, as well as other relevant quality aspects in support of the proposed approach.	
332	L190-198	24	<p>Comment:</p> <p>Could a commercially available syringe/pen/auto-injector which is used to manufacture a DDC be considered a “platform technology”?</p> <p>Proposed change (if any):</p> <p>If so, it should be made clear whether a letter of authorisation in compliance with Annex II of the guideline would suffice the quality requirements of the medical device part in the MAA dossier.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.
333	L192-193, L699-701 and L812-815	16	<p>Comment: ...data for those aspects of the device which pertain to the ‘platform’ should be presented. Definition for platform technology does not provide enough information in 699-701.</p> <p>Proposed change (if any):</p> <p>Since Integral DCC as described in row 68 “intended exclusively for use in the given combination” includes testing in the given final combination (e.g. as per ISO 11608-series) more guidance is needed on what can be considered be platform data that could be used in the context described and intended, including Annex 2 point 2.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
334	L195-197	31	<p>Comment:</p> <p>It is acknowledged that reference can be made to previously approved DDC which can provide “supportive information” to another DDC. However, it should be noted that an identical device may need no further testing, or a justification could be provided in a MAA or variation and reviewed by the drug competent authority.</p> <p>Proposed change:</p> <p>Consider providing further guidance on what would be supportive or whether certain prior approvals of DDCs would provide conclusive evidence obviating the need for a new NBOp.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.
335	L195-198	23	<p>Information about a device that formed part of a previously approved drug-device combination does not guarantee its quality and safety when combined with a different drug. The idea that technical equivalence, within the meaning of the regulations on medical devices, is transposable from one medicinal product to another could lead to unsafe drug-device combinations.</p>	The comment is acknowledged, the text has been modified.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
336	L196-198	14	<p>Comment:</p> <p>Use of the term 'platform' requires elaboration.</p> <p>The definition in Section 10 only extends to technologies that have previously been approved for another medicinal product.</p> <p>Previously approved DDCs may also be extended to products not marketed by the MAH. E.g.: syringes barrels used by several pharma companies.</p> <p>References to the DDC that are already approved and developed by the Marketing Authorisation holder (MAH) could be acceptable. However, the medicines company may not hold the Authorisation for this platform device. It will be appreciated if a clarification would be added regarding the use of previously approved platforms (with any other MAH) by providing adequate reference.</p> <p>Proposed change (if any): Consider EMA expectations for the kind of 'discussion' and 'justification' needed from the Applicant in these two different cases of platforms. Could it be considered that a NBOP could be obtained for "platform" technologies such as a pre-filled syringe by the technology manufacturer. The MAH could reference this for their specific medicinal product in its own NBOP.</p>	The comment is acknowledged, the text has been modified and no longer mention platform technology.
4.4. GENERAL CONSIDERATIONS – SCIENTIFIC ADVICE (L199-204)				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
337	L200-204	14	<p>Comment:</p> <p>Further clarification is requested regarding the procedural aspects of such advice, specifically involvement of Notified Bodies (commercial entities) in Scientific Advice to ensure alignment of requirements.</p> <p>Proposed change (if any): It will be appreciated for medicines Competent Authorities to develop provisions for joint scientific advice with the CA, device competent authority and NB/MDCG for new innovative technologies.</p>	The comment is acknowledged; however, this is outside the scope of the guideline.
338	L203-204	14	<p>Comment:</p> <p>For consistency of reference to "CA".</p> <p>Proposed change (if any): Consideration should be given to seeking advice within the EU network of CAs Competent Authority for regulation of medicines-network early in development, particularly for new and/or emerging technologies (see Section 9).</p>	The comment is acknowledged, the text has been modified.
339	L203-204	23	<p>Comment:</p> <p>Rather than speculating about emerging technologies, it seems far more urgent to form and operate a European committee for medical devices vigilance, similar to the European pharmacovigilance network</p>	<p>The comment is outside the scope of this guideline.</p> <p>The references to "speculation" when referring to emerging technologies and comparison with device vigilance are not agreed.</p> <p>EMA does not authorise or regulate medical devices</p>
340	L204	19	<p>Comment:</p>	The comment is acknowledged; however, this is outside the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>It may also be pertinent to seek advice from a Notified Body or device competent authority.</p> <p>Proposed change (if any): Include these options.</p>	
<u>5. INTEGRAL DDCs – 5.1. MODULE 1, PRODUCT INFORMATION (L205-225)</u>				
341	L205	14	<p>Comment:</p> <p>Electronic product information is an important future development and any new guideline that describes aspects of labelling should also consider these new developments.</p> <p>Proposed change (if any):</p> <p>Add a cross-reference to the EMA-HMA-EC document “Electronic product information for human medicines in the EU – draft key principles”</p>	The comment is acknowledged but is outside the scope of this guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
342	L206	3	<p>Comment:</p> <p>Based on precedence for product information for other integral DDCs, it is suggested to add a description for the device into section 3 of the SmPC.</p> <p>The Directive states that for implantable devices there should be information included on any health risk warnings or precautions to be taken, e.g. compatibility with certain diagnostic devices with or without scanners used for security purposes (Section 6.2 of the SmPC and corresponding sections of the PIL)</p> <p>Proposed change (if any): Add a reference to Section 3 of the SmPC as per the above comment.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
343	L206	14	<p>Comment:</p> <p>Suggest that the SmPC guidance and QRD templates be updated since this should be the primary source and SmPC content generation is typically led by labelling experts who will not be referring to DDC-specific guidance.</p> <p>If the SmPC guidance update is not possible, the primary SmPC guidance should at least be cited here.</p> <p>Proposed change (if any):</p> <p>Cite the primary source guidance and position the text in 5.1 as additional recommendations. http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
344	L206	21	<p>Comment:</p> <p>Please if is it possible to add a new version of the standard template for SmPC, package leaflet and labels, updated word version, as annex of this guideline.</p>	The comment is acknowledged. A hyperlink to the QRD documents has been included.
345	L206 and	35	<p>Comment:</p> <p>With reference to "5.1. Module 1, Product Information", it is recommended to update the SmPC guidance, accordingly, in order to capture all the infos regarding the use of a device (as integral and non integral DDCs).</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
346	L207	14	<p>Comment:</p> <p>SmPC section 1 - define 'device presentation' in section 10 for clarity</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
347	L207	14	<p>Comment:</p> <p>The SmPC guidance discourages mention of the route of administration or container (i.e. device) unless there is a specific reason to include e.g. patient safety, differentiation or the item is part of the standard term. For the first MAA, the device term is not always included because it can fail to meet these criteria. There are some device technologies where EDQM does not include a specific term or suitable term. If the intent of this statement is simply to clarify that the device term should comply with EDQM rules and is not a recommendation to include the device term in every case, the following change is proposed.</p> <p>Proposed change (if any):</p> <p>Rephrase 'Where the device presentation is included in the name of the medicinal product this should align with EDQM standard terminology for pharmaceutical form as far as available'.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
348	L207	24	<p>Comment:</p> <p>There is no requirement that the name of the medicinal product should include the integral device presentation. Sometimes the device represents the pharmaceutical form, but this is not valid for every medicinal product.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
349	L208	19	<p><u>Comment:</u></p> <p>There are some device technologies where EDQM does not include a specific term or suitable term.</p> <p><u>Proposed change (if any):</u></p> <p>Clarify use of EDQM terminology where it exists, otherwise clearly describe the device technology.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
350	L209 and L481	14	<p><u>Comment:</u></p> <p>SmPC Section 4.2 - per current guidance, assumed that this description would be under the 'Method of Administration' subheading - It is suggested to state that for clarity. Please also clarify in this section that a cross-reference to 6.6 or the Package Leaflet is still acceptable for further practical details on the method of administration (per QRD template guidance).</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
351	L209-210 and L481	14	<p>Comment:</p> <p>Section 4.2 of the SmPCs focuses primarily on defining doses and target population.</p> <p>Directions for proper use, such as cleaning is proposed to be included in section 6.6 along with "Information on instructions for preparation or reconstitution" placed in section 6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' (or in section 12 if appropriate) and cross-referenced here" (as per SmPC guideline).</p> <p>It might also be appropriate (justified by the result of usability evaluations) to refer in a SmPC section to a parallel provided standalone IFU (e.g. in case of having a lay user) in cases where handling steps are more complex.</p> <p>Proposed change (if any):</p> <p>SmPC Section 4.2: The doses and target (patient) population directions for proper use of the DDC should be described (including cleaning of the device as necessary), in line with relevant guidance. A device tradename may be stated. Reference to section for preparation and handling instructions (refer to SmPC section 6.6.) for the DDC should be provided.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
352	L210	14	<p><u>Comment:</u></p> <p>'Relevant guidance' for directions for proper use, is not elaborated. Might be located to SmPC 6.6 according to previous comment.</p> <p><u>Proposed change (if any):</u></p> <p>Include reference to the relevant guidance(s) EMA has in mind. Clarify where necessary whether this should be device guidance; or drug guidance; or both.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
353	L210	14	<p><u>Comment:</u></p> <p>The inclusion of 'device tradename' should be clarified. Many device-suppliers seek a trademark for their technology. However, this is not necessarily carried forward to an Applicant's tradename associated with the Medicinal Product. It is assumed that EMA wish to see any product-related device tradename, however this is not clear.</p> <p>Inclusion of tradename of the device in the SmPC should be restricted to specialist devices only that have been used for testing with the medicinal product performance.</p> <p><u>Proposed change (if any):</u></p> <p>Clarify the requirement is for any product-related device tradename.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
354	L210	19	<p><u>Comment:</u></p> <p>'Relevant guidance' for directions for proper use, is not elaborated.</p> <p><u>Proposed change (if any):</u></p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Include reference to the relevant guidance(s) EMA has in mind. Clarify where necessary whether this should be device guidance; or drug guidance; or both.	
355	L210	19	<p>Comment:</p> <p>The inclusion of 'device trademark' should be clarified. Many device-suppliers seek a trademark for their technology; however, this is not necessarily carried forward to an Applicant's trademark associated with the Medicinal Product. It is assumed that EMA wish to see any product-related device trademark, however this is not clear.</p> <p>Proposed change (if any):</p> <p>Clarify the requirement is for any product-related device trademark.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
356	L211	19	<p>Comment:</p> <p>Text states inclusion 'where relevant'. It is assumed that there will always be a need to include in-use shelf-life.</p> <p>Additionally, product shelf-life comprises two essential components – that data associated with the device function and performance over time ('functional stability', device aging data); and the data associated with the medicinal product shelf-life in container (traditional 'stability').</p> <p>Proposed change (if any):</p> <p>Remove 'where relevant' unless including specific examples to clarify where this is not needed. Clarify that in use shelf-life must suitably consolidate both device and medicinal product data.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
357	L211	14	<p><u>Comment:</u></p> <p>Unless shelf-life of the device component is shorter than that of the drug product (which is rare in our view), only the shelf-life information on the active should be stated in the SmPC Section 6.3. Would the agency agree?</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
358	L211	14	<p><u>Comment:</u></p> <p>Text states inclusion 'where relevant'. It is not clear when in-use shelf-life is needed; clarify with example.</p> <p><u>Proposed change (if any):</u></p> <p>Including specific examples to clarify where this is not needed.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
359	L211	24	<p><u>Comment:</u></p> <p>Section unclear. An integral DDC will not have an in-use shelf-life of its own.</p> <p><u>Proposed change (if any):</u></p> <p>Delete the information in line 211.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
360	L212	14	<p><u>Comment:</u></p> <p>Storage condition of the integral DDC should not differ and the requirements for the QRD text should be followed.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
361	L213 and L485	8	<p>Comment:</p> <p>We consider it should be sufficient, when such components are listed and potentially explained, which have either an impact on the quality, safety and efficacy of the whole product or which may impact the safety, performance and usability of the device.</p> <p>Justification: Also for excipients, there are exemptions for providing full information in the SmPC, depending on the route of admiration (see EurdaLex – Notice to applicants Volume 2C, “Excipients in the labelling and package leaflet of medicinal products for human use” page 3 “EXCIPIENTS IN THE LABELLING”), for this reasons it seems not so clear why for Medical Devices all components should be listed without consideration of its effects on the general product performance.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
362	L213	9	<p>Comment:</p> <p>Harmonizing the nomenclature of DDC's device-constituent(s) basing on existing medical devices nomenclature databases would both support leveraging NBOP for platform technologies, and help device-constituents and DDC manufacturers with establishing state of the art required under MDR 2017/745 Annex I on GSPR. See also the General comment on harmonization.</p> <p>Proposed change (if any):</p> <p><i>SmPC Section 6.5: The type of the device-<u>constituent(s)</u> <u>and its (their) component material(s)</u> should be listed, <u>considering recognized medical device database nomenclature (CND codes, GMDN codes)</u></i></p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
363	L213	10	<p>Clarification:</p> <p>This may be straightforward for a DDC - container closure system, however, others may have complex construction so providing all components of materials may not be value adding. Should this be applicable to product contacting surfaces or components critical to the function of the device?</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
364	L213	14	<p>Comment:</p> <p>It is not clear why the guidance requests information on component materials. Device component materials are not always relevant to the drug product.</p> <p>It is perhaps more reasonable for the guidance to request information pertaining to the material used in those components that are in transient- or storage-contact with medicinal product; and those in potential contact with the user of the product. Internal 'non-contacting' component materials should not be of interest to the medicine competent authority. All device materials will be within the scope of a Notified Body or Manufacturer assessment against GSPR #7.</p> <p>Proposed change (if any):</p> <p>Only high-level information on material of construction of the device should be included rather than the detailed composition, e.g. 'plastic device'. Clarify to state "patient-contact materials or material as of concern as identified in the risk assessment and GSPR, i.e. Latex.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
365	L213	19	<p>Comment:</p> <p>It is not clear why the guidance requests information on component materials. Device component materials are not always relevant to the drug product.</p> <p>It is perhaps more reasonable for the guidance to request information pertaining to the material used in those components that are in transient- or storage-contact with medicinal product; and those in potential contact with the user of the product. Internal 'non-contacting' component materials</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>should not be of interest to the medicines competent authority.</p> <p>All device materials will be within the scope of a Notified Body or Manufacturer assessment against GSPR #7.</p> <p>Proposed change (if any):</p> <p>Consider being more specific regarding device component materials.</p>	
366	L213	24	<p>Comment:</p> <p>This information is not relevant to be included in SmPCs or leaflets. It is not necessary to instruct a doctor and may not be interpretable by patients. Furthermore, this information is already part of the registration file ("Extractables and Leachables").</p> <p>In addition, it goes beyond the requirements for labelling of a medical device (see GSPRs).</p> <p>Proposed change (if any):</p> <p>Delete.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
367	L213	28	<p>Comment:</p> <p>The type of the device(s) and its (their) component material(s) should be listed (in SmPC). This should be limited to the device materials in drug contact – otherwise it is Not in line with the core precept of lines 155-157</p> <p>Proposed change (if any):</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The type of the device(s) and its (their) component material(s) in contact with the drug should be listed.	
368	L213	31	<p><u>Comment:</u></p> <p>There is a reference here to “type of device”.</p> <p><u>Proposed change (if any):</u></p> <p>Under the MDR, device types will be indicated by their medical device nomenclature (i.e. CND code). It would improve consistency between EMA and NBs if the device code was used in both places, especially for market surveillance purposes.</p> <p>Please also consider the applicability of CND codes for DDCs. In addition: CNDs are developed for medical devices but will there also be CND codes that are applicable for the device constituent part of DDCs?</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>The revised text also includes clarification that the product information of a medicinal product with an integral medical device should not include any administrative information on the medical device.</p>
369	L214	28	<p><u>Comment:</u></p> <p>This paragraph should be more specific, as this section is not to include the handling of the medical device. The current phrasing could be misunderstood.</p> <p><u>Proposed change (if any):</u></p> <p>Brief explanation on the recommended handling of the integral DDC such as reconstitution and disposal.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
370	L214	14	<p><u>Comment:</u></p> <p>Add cleaning and include the comments on the relevant guidance (see 4.2, line 210).</p> <p><u>Proposed change (if any):</u></p> <p>SmPC Section 6.6: Product-specific information should be provided for preparation and/or handling and proper use of the DDC (including cleaning and disposal of the device(s) as necessary)</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
371	L214 and L486	14	<p><u>Comment:</u></p> <p>SmPC Section 6.6 - please clarify in this section that a cross-reference to the Package Leaflet is acceptable for further practical details (per QRD template guidance in section 4.2).</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
372	L216	14	<p><u>Comment:</u></p> <p>The inclusion of the IFU information in the PIL will require modification of current QRD requirements. If this is the case, it will be useful to include a general requirement for the overlap. The guidance does not elaborate how 'clear'; 'simple'; 'consistent with' will be assessed; or by whom. Similarly, it is not achievable to completely 'prevent' medication errors. Device instructions will be assessed by the Manufacturer/Notified Body against several GSPRs, including #13.</p> <p>Approach is to append the full IFU at the end of the Package Leaflet. The IFU is then included in packs in booklet form or printed leaflet. It might also be appropriate (justified by the result of usability evaluations) to refer in a SmPC section to a</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents. Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>parallel provided standalone IFU (e.g. in case of having a lay user) in cases where handling steps are more complex.</p> <p>As per Art 63(2) of EU Directive 2001/83/EC as amended, readability testing of the PIL is needed.</p> <p>A clarification on how the information on the DDC usage (taken from the IFU) should be included as part of readability testing and/or if the Usability testing of device by Human factor study could supplement this requirement.</p> <p><u>Proposed change (if any):</u></p> <p>Clarify the information content being discussed in this section and the distinction to that information being reviewed under the relevant MDR Annex I GSPRs.</p> <p>Addition after line 219:</p> <p>Alternatively, the full IFU can be included after the package leaflet text or as stand-alone IFU as justified by the usability evaluation.</p>	
373	L216	1	<p><u>Comment:</u></p> <p>It is important that patients understand the use of the devices perfectly, so the information given to users should have been tested and appropriate to the different levels of patient literacy. The presence of pictograms on leaflets explaining the handling of the devices should be mandatory. Another aspect to include could be the one related to frequent errors of use of the device that critically affect to obtain a greater pulmonary deposit. In addition to explaining how the cleaning of the device is done and why it should be done so.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>It has been clarified that information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
374	L216-219	23	<p>Comment:</p> <p>Package leaflets should certainly be consistent with, but not less informative than, the SmPC. Yet this is often the case, especially with regard to adverse effects and warnings.</p> <p>Package leaflets should not be "simple". They must be sufficiently detailed and must then undergo readability testing by patients and/or professionals.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
375	L216-219	19	<p>Comment:</p> <p>It is not clear whether EMA are suggesting that for integral DDCs it is mandatory to integrate the PIL and IFU, or whether this is optional.</p> <p>Proposed change (if any):</p> <p>Clarify this point via suitable language.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>
376	L216-219	27	<p>Comment:</p> <p>EFA would like to highlight the fundamental link between the SmPC and the Package Leaflet for both integral and non-integral DDCs. Although the SmPC is procedurally aimed only at healthcare professionals, it should be made clear that it is the origin of all the information that is included in the Package Leaflet, and therefore arrives at the end users i.e. the patients. Unclear or insufficient information in the SmPC may have an impact in the Package Leaflet content, potentially putting patients' health at risk, especially in life-threatening situations such as during a severe asthma attack or an anaphylactic shock. EFA considers it is critical to ensure that SmPCs are designed for the market authorisation applications (MAAs) in the most accurate and comprehensive manner. This</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			issue is essentially linked to health literacy, which should also be seriously taken into consideration. To prevent wrongful and potentially dangerous use/administration of a DDC, given instructions should be simple, readable, and –to the extent possible- supported by photos and videos. Drawings or other visual representations of the correct use of inhalers can also be helpful.	
377	L216-219	27	<p>Comment:</p> <p>Now that EMA develops the basic principles for an electronic Product Information, it would be very useful for patients to access graphic information on how to use DDCs drawn from online sources. It is important that this information is the result of a collective effort involving healthcare professionals, the pharmaceutical industry, patients (patient associations such as EFA and patient experts as such, both at the EU and local level), but also interdisciplinary workers such as physicians, nurses, informal care givers should be taken into account, along with family members. Finally, organisations that support people with low health literacy need to be involved.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
378	L216-219	27	<p>Comment:</p> <p>EMA should put an effort in solving the issue of contradictory leaflet information in equal devices. There have been several cases in the past where package information did not match between similar products e.g. nasal sprays, inhalers. Furthermore, in some inhaler devices the leaflet information is different compared to the local protocols used by health care organizations, e.g. in the Netherlands.</p>	<p>The comment is acknowledged.</p> <p>The text is not modified as the aim of this guidance is to provide general guidance on labelling aspects on the documentation expected for drug-device combinations.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): Promote uniformity in leaflet information.	
379	L216-218 and L220	19	<p>Comment:</p> <p>For combined products, the Patient Leaflet often incorporates Instructions For Use. The guidance does not elaborate how 'clear'; 'simple'; 'consistent with' will be assessed; or by whom. Similarly, it is not achievable to completely 'prevent' medication errors. Device instructions will be assessed by the Manufacturer/Notified Body against several GSPRs, including #13.</p> <p>Proposed change (if any):</p> <p>Clarify the information content being discussed in this section and the distinction to that information being reviewed under the relevant MDR Annex I GSPRs.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>
380	L217	19	<p>Comment:</p> <p>Typically, products of this mature are employed by a range of users, beyond patients and HCPs.</p> <p>Proposed change (if any):</p> <p>Change 'patients and/or for healthcare professionals (HCP)' to 'users'.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
381	L217	14	<p>Comment:</p> <p>Devices may also be used by caregivers, which has to be included as a user group above not just “patients and/or for healthcare professionals (HCP)”.</p> <p>Proposed change (if any):</p> <p>Included users in the user group “...lay users (such as patients), care givers and/or healthcare professionals”.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
382	L218	5	<p>Comment:</p> <p>Which aspects should be consistent with IFU? We assume just patient use instructions, but the requirements are slightly different for medicinal products and devices. For example, legal manufacturer, use of symbols.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
383	L219	2	<p>Comment:</p> <p>Health care providers frequently request placebos, which are used to train patients in how to use their inhaler. However, these are not readily available: many pharmaceutical companies have stopped this service. We need a solution to this.</p> <p>Leaflet information</p> <p>Comment:</p> <ul style="list-style-type: none"> - Please be aware that currently the package information for inhalers sometimes doesn't match. E.g. packages for equivalent nasal sprays provide contradictory information. It would be helpful to solve this issue. - Also, in some inhaler inhalers the Dutch leaflet information is different compared to the local Dutch protocols used by health care organizations. 	<p>The comment is acknowledged.</p> <p>The text is not modified as the aim of this guidance is to provide general guidance on labelling aspects. Specific product-related aspects are outside the scope of this guidance.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p><u>Proposed change (if any):</u></p> <ul style="list-style-type: none"> - Avoid contradictory information between inhalers (stipulate uniformity) - Check the importance of handling steps on inhaler proposition: is it really necessary to hold the inhaler straight up? Should it be shaken or not? Etc. In some cases there is variation in opinion between the drug company and scientists. <p>Leaflet information: involvement of patient organizations</p> <p><u>Comment:</u></p> <p>Patient organizations (e.g. ELF, EFA, EAACI patient group, but also local organizations). Also, organizations that support people with low health literacy need to be involved.</p> <p>Leaflet information: interdisciplinary workers</p> <p><u>Comment:</u></p> <p>The care for respiratory patients is multidisciplinary. Besides the professional caregivers like physicians and nurses, informal caregivers are also involved and need to be taken into account.</p> <p><u>Proposed change (if any):</u></p> <p>Some links for videos could be added so that the family or care givers could be involved in training where other sources aren't available</p> <p>Leaflet information: pharma companies</p> <p>The pharma company should be responsible for this, but it could be drawn from other sources and needs to be easily</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			assessable, practical and also test the impact on patient beliefs and behaviours.	
384	L220	3	<p>Comment:</p> <p>Subheading says “Package leaflet and labels”, but the text is referring to outer packaging and package leaflet.</p> <p>Clarification should be given to what kind of symbols they are referring to, to the Medical device symbols/ISO symbols?</p> <p>Proposed change (if any):</p> <p>Change subheading to “Package leaflet and labelling”. Information in line 216 to 219 could be included under this subheading as well, as it refers to the package leaflet.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
385	L220	3	<p>Comment:</p> <p>In the case of implantable devices which are considered DDC, clarity on whether an implant card would be required as part of the product information would be appreciated.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p>
386	L220	5	<p>Comment:</p> <p>Only symbols to clarify information see L218?</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>A clarification that the labelling for the integral DDC should follow the labelling requirements for medicinal products has been included.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
387	L220 and L492	31	<p>Comment:</p> <p>There is a reference to symbols used in labelling</p> <p>Proposed change (if any):</p> <p>Device regulation expectations include a harmonized standard for symbols, EN ISO 15223-1, which would be a consistent reference for symbols between groups.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>A clarification that the labelling for the integral DDC should follow the labelling requirements for medicinal products, and that MDR obligations related to UDI are not required and should not be applied to the package of the medicinal product has been included.</p>
388	L220-221 and L229-230	23	<p>Comment:</p> <p>SmPCs and package leaflets should describe devices in detail and give detailed instructions for use, with the aid of photos and/or illustrations. Package leaflets should include a diagram showing all the components of the package, with explanations indicated with arrows, and comments.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
389	L220-222	14	<p>Comment:</p> <p>Relevance and application of device labelling GSPRs when pursuing the NBOp route for an integral DDC is not clear.</p> <p>Change “patient” to user to encompass all categories of users (patients, caregivers and/or HCPs).</p> <p>The current wording may promote the use of non-standard and untested symbols which could cause confusion and/or lead to medication errors. What approach should be taken for mandatory safety symbols which must be applied to outer packaging in order to comply with Harmonised Standards? EN 60601-1, for example.</p> <p>Proposed change (if any):</p> <p><u>Package leaflet and labels:</u> The outer packaging and the Package Leaflet may include standard recognizable symbols or pictograms, to clarify certain information described in the SmPC (e.g. instructions for use) which may be useful for the user.</p> <p>Device and medicinal product labelling standards for symbol should be used (i.e. EN ISO 15223-1 for the device aspects). Any element of a promotional nature <u>should be excluded</u>.</p>	<p>The comment is acknowledged.</p> <p>The text has been deleted and replaced by general reference to applicable legislation, relevant guidelines and QRD documents.</p> <p>Information which is necessary for the use of the device must be included in the relevant sections of the package leaflet and SmPC. It has been clarified that MDR obligations related to UDI are not required and should not be applied to the package of the combination product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
390	L220-225	27	<p>Comment:</p> <p>As a general observation, apart from the package, EFA would see value in having instructions on the device itself e.g. 'shake/don't shake', 'keep upright', 'do not store in the bathroom' etc, possibly accompanied by illustrative pictures. This is because many patients do not read the leaflets but we also know that most patients make inhaler mistakes. Therefore, having some minor instructions on the inhaler might solve some problems in this respect. Given the rise of technology there are also smart applications to support these actions and also videos adapted to local circumstances. Moreover, providing some links for videos could also be considered, especially since they could prove useful to the family or care givers by involving them in training where other sources are not available.</p> <p>Also, EFA thinks that the package leaflet should contain detailed information on the parts of the device that are composed of or include allergen material e.g. latex.</p>	<p>The comment is acknowledged.</p> <p>The text is not modified as the aim of this guidance is to provide general guidance on labelling aspects. Specific product related aspects are outside the scope of this guidance.</p>
391	L223 and L406	14	<p>Comment: It is unlikely that an Integral DDC will have a CE mark.</p> <p>Proposed change (if any): Clarify providing an example OR delete for integral DDCs.</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations such as CE mark are not required and should not be applied to the package of the combination product. For integral devices with a CE mark, it may be assigned to the device itself, however it should not appear on the outer package of the medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
392	L223 and L494	14	<p>Comment:</p> <p>This line is confusing in that the reader could misinterpret the CE mark placement to include placing the CE mark on a CE marked injector that is part of an integral DDC. If the intent was that this requirement would apply to a non-integral CE marked device, then please clarify this statement. In this case the device is regulated according to MDR and must bear the CE-mark on the device.</p> <p>Article 20.3 MDR states: <i>“the CE marking shall be affixed visibly, legibly and indelibly to the device or its sterile packaging. Where such affixing is not possible or not warranted on account of the nature of the device, the CE marking shall be affixed to the packaging. The CE marking shall also appear in any instructions for use and on any sales packaging.”</i></p> <p>Further clarity is requested regarding how to handle a device part of the integral DDC or device of a non-integral DDC which does not have sufficient space for the CE mark on (as per Article 20 MDR the CE mark would have to be placed on the packaging): should the CE mark be included in the DDC PIL?</p> <p>Proposed change (if any):</p> <p>Move to non-integral and include after line 494: “For a non-integral device that has a CE mark, the CE mark should be included...”</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations such as CE mark are not required and should not be applied to the package of the combination product. For integral devices with a CE mark, it may be assigned to the device itself, however it should not appear on the outer package of the medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
393	L223	14	<p>Comment:</p> <p>It should be made clear the UDI is not a requirement for single integral DDCs as these are covered by medicinal product serialization.</p> <p>Proposed change (if any):</p> <p>Include in text that medicinal product serialisation will be in place of medical device UDI.</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations related to UDI are not required and should not be applied to the package of the combination product. Even if the integral device is CE marked, it is expected that the labelling for the integral DDC should follow the labelling requirements for medicinal products.</p> <p>For integral devices with a CE mark, the UDI may be assigned to the device itself, however the UDI should not appear on the labelling or outer package of the medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
394	L223-225	5	<p>Comment:</p> <p>It is outlined that "For a device <u>that has a CE mark, the CE mark may be included on the device itself</u> but should not be included on the labelling for the DDC as this may be interpreted incorrectly as referring to the DDC as a whole."</p> <p>This statement is a contradiction to the requirements outlined in the MDR (Article 10.6 and Article 20): all medical devices have to have a CE mark affixed in order to indicate that a medical device is in conformity with the applicable requirements of the MDD/MDR.</p> <p>The legislation currently does not specify medicinal product labelling requirements overrule MDR requirements with respect to labelling of CE marked devices.</p> <p>The legislative instruction should be clarified.</p> <p>Proposed change (if any):</p> <p>Change the statement in line 223 to "For a device <u>that has a CE mark, the requirements of article 20 Medical Device Regulation 2017/745 needs to be followed.</u>"</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations such as CE mark are not required and should not be applied to the package of the combination product. For integral devices with a CE mark, it may be assigned to the device itself, however it should not appear on the outer package of the medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
395	L223-225	18	<p>Comment:</p> <p>For an integral DDC the device component would not be able to be CE-marked as the DDC is regulated as a medicinal product and not a medical device with an MDR designated NB unable to accept an application or issue an CE Certificate for the device in this integral combination.</p> <p>Proposed change (if any):</p> <p>Remove the sentence as existence of the CE-mark on the Integral DDC would also lead to the incorrect interpretation of the regulatory status of the device.</p> <p>For a device that has a CE mark, the CE mark may be included on the device itself but should not be included on the labelling for the DDC as this may be interpreted incorrectly as referring to the DDC as a whole.</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations such as CE mark are not required and should not be applied to the package of the combination product. For integral devices with a CE mark, it may be assigned to the device itself, however it should not appear on the outer package of the medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
396	L223-225	19	<p>Comment:</p> <p>Once again, it is unclear how/why the integral device constituent should carry a CE-mark. This would effectively label the medicinal product as a product with Medical Device primary mode of action.</p> <p>For an integral DDC, there is typically only one label, and in this configuration this would be defined by pharmaceutical labelling legislation. No CE-mark should appear anywhere on the device constituent.</p> <p>Additionally, a CE-markable/CE-marked device constituent of an integral product would require conformance with EUDAMED & UDI requirements in order to achieve its CE-certification. However, as a Medicinal Product, pharmaceutical requirements would require serialisation. This has the potential to cause confusion both in industry and to the market.</p> <p>Proposed change (if any):</p> <p>Clarify this point throughout the document.</p>	<p>The comment is acknowledged.</p> <p>It has been clarified that when the device is governed by the medicinal products legislation, then MDR obligations such as CE mark are not required and should not be applied to the package of the combination product. For integral devices with a CE mark, it may be assigned to the device itself, however it should not appear on the outer package of the medicinal product.</p>
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.1 – DESCRIPTION AND COMPOSITION (L227-230)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
397	L227, L231 and L243	14	<p>Comment: All 3 chapters require description of the device and/or the justification of suitability of the device for the specific drug product. Such redundancy should be avoided; a single section should be selected to contain the description and suitability of the integral device(s) used with the drug product. Recommend to provide the device description section to another section such as 3.2.R, and reference from 3.2.P.1 and P.2 sections to 3.2.R and delete additional high level description of the DDC from P.2.1.</p> <p>It is recommended that more flexibility should be allowed as to how that information is spread across those subsections.</p>	The comment is acknowledged. However, it was decided to keep the three different sections and to follow the CTD structure to have more consistency between files and facilitate assessment.
398	L228	14	<p>Comment:</p> <p>Please define what is meant by “concise” and specify by example the information to be included.</p>	The comment is acknowledged, however, no update to the guideline is proposed.
399	L228-231	28	<p>Comment:</p> <p>“and if applicable, any additional devices provided and used with the medicinal product, should be submitted. The description and function of each device should be stated.” This should rather be limited to 3.2.R, as it is not directly related to the drug product.</p>	<p>The comment is acknowledged.</p> <p>Devices provided and used with the medicinal product are considered to be an intrinsic requirement for the correct use of the medicinal product, thus some information is required. The text has been slightly revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
400	L229-230	14	<p>Comment:</p> <p>It is mentioned that the description and function of each device should be stated in P.1.</p> <p>Description and function of the device is already provided in P.7 Container Closure System</p> <p>Proposed change (if any):</p> <p>Add the following: A reference to P.7 or cross-referral to 3.2.R could be included in P.1 to avoid redundancies across the dossier.</p>	<p>The comment is acknowledged.</p> <p>This requirement is based on Annex 1 of the Directive 2001/83/EC. No change is made.</p>
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.2 – PHARMACEUTICAL DEVELOPMENT (L231-312)</u>				
401	L231	28	<p>Comment:</p> <p>Expectations go way beyond the need for evaluation of the drug and can lead to “Design Freeze” that prevents continual improvements that is crucial for medical devices. Design control including ergonomic features are already part of the NBOp, there is no need to require additional documentation.</p> <p>Proposed change (if any):</p> <p>Add:</p> <p>If documentation of compliance to a requirement is included in NBOp, this NBOp can be referred. There is no need to duplicate sections covered by NBOp.</p>	<p>The comment is acknowledged. The text has been slightly modified. However, CA and NB assess the device from different perspectives as stated in the guideline.</p> <p>“The core precept of this guideline is that the CA responsible for the regulation of medicines will evaluate the device (part) specific aspects relevant to the quality safety and efficacy (and hence overall benefit/risk determination) of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs for the device (part).”</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
402	L232-233	24	<p>Comment:</p> <p>It is not appropriate to include information on the development of the device into section P.2, but information on the development of the medicinal product.</p> <p>Proposed change (if any):</p> <p>“This section of the dossier should summarise all information relevant for the device as integrated into the medicinal product, including the rationale for its selection.”</p>	<p>The comment is acknowledged.</p> <p>The CA need to understand changes made during development, and why. The text has been slightly modified.</p>
403	L232-236	19	<p>Comment:</p> <p>‘all information relevant to the development of the device’ is a very broad consideration. Similarly, ‘narrative of device... development including all relevant data... should be provided’ is equally broad. Both sentences are open to interpretation.</p> <p>Proposed change (if any):</p> <p>It would be beneficial to industry for the guideline to be more specific in this respect, especially when similar development type information is likely to have been reviewed against the relevant MDR Annex I GSPRs.</p>	<p>The comment is acknowledged, the text has been modified.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
404	L232-240	14	<p>Comment: It is not clear if an introduction that outlines the content of 3.2.P.2 is being proposed. It would be more helpful if the expectations for 3.2.P.2 were in the individual subsections to avoid duplication and unnecessary additional text. This text seems redundant.</p> <p>Proposed change (if any):</p> <p>"This section of the dossier should summarise all information relevant to development of the device as integrated into the medicinal product, including the rationale for its selection in the specific sections. The suitability of the device for its intended use, in the context of the device performing as intended and protecting the medicinal product etc., should be demonstrated. A clear narrative of device and medicinal product development including all relevant data (e.g. justification of any new device, pharmaceutical form, etc.) should be provided.</p> <p>The suitability of the DDC and its materials of construction to protect the drug product formulation from light, moisture, microbial contamination and vapour phase permeation (as appropriate) should be confirmed. Any interactions of the device with the medicinal product should be discussed and justified, as appropriate."</p>	The comment is acknowledged; the guideline text has been amended accordingly.
405	L235-237	24	<p>Comment:</p> <p>It is not appropriate to include information on the development of the device into section P.2, but information on the development of the medicinal product.</p>	The comment is acknowledged The text has been modified to state integral medicinal product in stead of device.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p><u>Proposed change (if any):</u></p> <p>Delete.</p>	
406	L236	22	<p><u>Comment:</u> It is not clear what 'new' means. We assume that 'new' means the selected device has never been marketed anywhere in the world.</p> <p><u>Proposed change (if any):</u> ... justification of new-device that has not been marketed before ...</p>	The comment is acknowledged, the text has been modified.
407	L239-240	24	<p><u>Comment:</u></p> <p>Leachables, extractables</p> <p>It is fulfilled by the Directives for medicinal products. Is not necessary for the device part in the integral DDC to fulfil the requirements for medicinal products and for medical devices.</p> <p>See also comments on line 211.</p> <p><u>Proposed change (if any):</u></p> <p>Delete.</p>	The comment is acknowledged, the text has been deleted.
408	L241	14	<p><u>Comment:</u> ICH Q9 and ISO 14971 are both guidelines for Risk Management. It is assumed that EMA seeks a risk management summary (rather than just a 'risk assessment' summary). The former is more likely to explain the principles adopted during risk management, identification of hazards and harms, outcomes of risk assessment, residual risk levels and a final risk-benefit analysis and intentions for post-market risk management. A risk assessment summary would not necessarily incorporate these other aspects. It might be</p>	The comment is acknowledged, the text has been modified, ISO 14971 has been excluded.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>valuable to provide more guidance on the level of detail which might be expected. (ICH Q9 vs ISO14971)</p> <p>Risk assessment of the device constituent part according to EN ISO 14971 is assessed by the NB and therefore reflected in the NB opinion. Therefore, cross-referral may be an appropriate option.</p> <p>The DDC risk assessment should focus on the drug and the impact the device may have on the drug and its delivery.</p> <p>It is requested that the guidance indicates where the risk assessment should be located.</p> <p>Proposed change (if any): "It is recommended that a risk assessment management summary for the DDC, aligned with suitable risk assessment management principles in ICH Q9 and/or DIN EN ISO 14971, is presented in the 3.2.P section or cross-referral to 3.2.R may be appropriate."</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
409	L241	10	<p>Comment:</p> <p>Risk assessment summary to be provided in P.2 would contradict the eCTD specification requirements.</p> <p>Proposed change (if any):</p> <p>We suggest providing the overall device risk management summary (process, design and user) in M3.2.R to keep all risk evaluations in one location and comply with eCTD specifications.</p>	<p>The comment is acknowledged, however, no update to the guideline is proposed. The GL also states:</p> <p>“To avoid repetition, it is acceptable to cross-reference between sections.”</p>
410	L241	19	<p>Comment: ICH Q9 and ISO 14971 are both guidelines for Risk Management. It is assumed that EMA seek a risk management summary (rather than just a ‘risk assessment’ summary). The former is more likely to explain the principles adopted during risk management, identification of hazards and harms, outcomes of risk assessment, residual risk levels and a final risk-benefit analysis and intentions for post-market risk management. A risk assessment summary would not necessarily incorporate these other aspects.</p> <p>Proposed change (if any):</p> <p>Change ‘risk assessment’ to ‘risk management’ (twice).</p>	<p>The comment is acknowledged, the text has been modified.</p>
411	L241	35	<p>Comment:</p> <p>With reference to the risk assessment summary, it is not clear which are the expectations and the degree of detail to be used in the regulatory documentation. Please clarify. Also clarify if it is mandatory to provide the risk-benefit ratio evaluation supported by the relative FMEA analysis.</p>	<p>The comment is acknowledged but is outside the scope of this guideline to add such specific guidance. Reference is made to applicable legislation, relevant guidelines and QRD documents.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
412	L241-242	25	Comment: Risk of duplication or conflicting data, if applicant does not clearly distinguish between datasets and how it is presented to NB and the drug authority.	The comment is acknowledged, the text has been modified, ISO 14971 has been excluded.
413	L242	8	The risk management file according DIN EN ISO 14971 is subjected to high scrutiny by the Notified Bodies frequently resulting in substantial influences of the device design, manufacturing and labelling. For this reason, we recommend to clarify in the guideline, how potential conflicts between Notified Body and Competent authority may be settled, when the relevant authority comes to a conflicting opinion concerning the evaluation of certain risks and its mitigation measures. Particularly, we would expect, that the guideline should provide advice on the possibilities to address such conflicts either by the MAH and/or the device manufacturer. We also recommend to provide particulars on the role of the authorities to resolve the ramification of such conflicting opinions.	The comment is acknowledged, the text has been modified, ISO 14971 has been excluded.
414	L242	14, 16, 31	Comment: Please refer to EN standards (harmonised) in general instead of the German version. Proposed change (if any): Replace "DIN EN ISO 14971" by "EN ISO 14971"	The comment is acknowledged, the text has been modified, ISO 14971 has been excluded.
415	L242	28	Comment: Applicants need not use the german version of the EN standard Proposed change (if any): Edit to read: "... ICH Q9 and/or EN ISO 14971, is presented"	The comment is acknowledged, the text has been modified, ISO 14971 has been excluded.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
416	L243-245	14	<p>Comment: The device is essentially like the container closure. 2.P.2.1 "Components of the drug product" describes the drug substance and the excipients or with other drug substances and does not normally describe the container closure system. A high-level description of the DDC is also considered redundant with P.1. The comment is acknowledged, the text has been modified.</p> <p>Proposed change (if any): Delete the following: P.2.1 Components of the Drug Product A high-level description of the DDC should be provided, cross-referring to other sections as appropriate.</p>	The comment is acknowledged, the text has been deleted.
417	L244-245	10	For a better understanding, a definition/explanation of the term "high-level" will be helpful ("A <i>high-level description of the DDC should be provided</i> ").	The comment is acknowledged, the text has been deleted in relation to comment 416.
418	L246-253	14	<p>Comment:</p> <p>The device is essentially similar to the container closure in how and where information needs to be presented in the CTD.</p> <p>P.2.2 contains information about the drug product and is meant to discuss formulation development, overages and characteristics, and is irrelevant of how the DP is administered.</p> <p>Any development data related to the device should be in P.2.3, and considerations for suitability in P.2.4. Any data comparing DDC prototype to marketed DDC therefore belongs to P.2.3. Cross-references to data in Module 4 or Module 5 can be provided in 3.2.R.</p>	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any): Propose delete the following from here and move it all to P.2.3. with an option to cross reference to appropriate sections such as P2.4 or 3.2.R.</p> <p><i>P.2.2-Drug-Product</i> The applicant must take into consideration the intended use of the device and its suitability within the context of the DDC, its therapeutic indication and the relevant target patient population. Where required (e.g. due to changes in device design during development), summary bridging data 249 (see Section 7) should be provided in this section of the dossier, with cross references to relevant data in Module 4 or Module 5, as appropriate. Appropriate data should be provided to demonstrate and justify the equivalence of the overall performance of the DDC prototype(s) used during pivotal clinical development with the DDC intended for marketing.</p>	
419	L249-253	14	<p>Comment: The bridging information may also be referenced from Module 3 (for technical bridging for relevant design changes).</p> <p>Proposed change (if any): Where required (e.g. due to changes in device design during development), summary bridging data (see Section 7) should be provided in this section of the dossier, with cross-references to relevant data in Module 3, Module 4 or Module 5, as appropriate.</p>	The comment is acknowledged, the text has been modified.
420	L249-253	14	<p>Comment: "Appropriate data" could be further defined (this could be nonclinical, clinical, and/or HF data). Additionally, a presumption should not necessarily be made that a "DDC prototype" was used during pivotal clinical studies; there may be other pathways (such as using a "bridging study" to move</p>	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>between completely different delivery devices – such as a PFS in pivotal, and AI or pen in a PK bridging study.</p> <p>Note that the bridging aspects also appear elsewhere (e.g. lines 258-259).</p> <p>Proposed change (if any): "Appropriate data should be provided to demonstrate and justify the equivalence of the overall performance of the DDC prototype(s) or delivery devices used during pivotal clinical development with the DDC intended for marketing.</p>	
421	L254	14	<p>Comment: The text concentrates upon the DDC manufacturing process.</p> <p>It is assumed that device constituent manufacturing processes are therefore out of scope (reviewed under relevant MDR Annex I GSPRs), however this should be clarified.</p> <p>Where the 'DDC manufacturing process' includes final assembly steps for the device constituent, the requirements for coverage of this in the MAA dossier should be clarified.</p> <p>Duplication of review could be reduced if the dossier focused on the process where the drug and device are combined. For example, final assembly/aseptic filling.</p> <p>A "concise" description should be restricted to development and sterilisation of the completed device sub-assembly(ies) to generate the DDC product.</p> <p>A brief outline for the subassemblies may be appropriate in the CTD drug product sections.</p>	The comment is acknowledged; the guideline text has been amended accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
422	L254	19	<p>Comment: The text concentrates upon the DDC manufacturing process. It is assumed that device constituent manufacturing processes are therefore out of scope (reviewed under relevant MDR Annex I GSPRs), however this should be clarified.</p> <p>Where the 'DDC manufacturing process' includes final assembly steps for the device constituent, the requirements for coverage of this in the MAA dossier should be clarified.</p>	The comment is acknowledged; the guideline text has been amended accordingly.
423	L254-260	20	<p>Comment: We assume that this section refers to information on manufacturing process development as it relates to the incorporation of the device with the medicinal product in order to achieve the desired characteristics for the combined product, and not to the manufacturing process development of the device <i>per se</i>.</p> <p>Proposed change (if any):</p> <p>Please clarify the above.</p>	The comment is acknowledged; the guideline text has been amended accordingly.
424	L256	14	<p>Comment: It is mentioned that the development, justification and suitability of sterilisation process of any devices or the DDC should be described in P.2.3.</p> <p>All suitability studies (including sterilisation of the device) could rather be provided in section P.2.4 to avoid dispersion of device specific information in P.2 sections. In addition, redundancies with section 3.2.P.3.5 should be avoided (where it is also suggested to present the validation of the sterilisation of the devices – refer to line 340).</p>	The comment is acknowledged, the text has been modified.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
425	L254-259	14	<p>Comment: The comparison of the manufacturing process for DDC from pivotal or bridging clinical studies and commercial DDCs should only include physicochemical comparison if there is a need to perform bridging clinical studies.</p> <p>Also, move text (line 249-253) from P.2.2 to P.2.3 and merged. This text relates to changes and hence falls under 'development'.</p> <p>Proposed change (if any):</p> <p><i>P.2.3 Manufacturing Process Development</i></p> <p>A concise description of the DDC manufacturing process development should be described in line with relevant guidance.</p> <p>The development, justification and suitability of sterilisation processes of any devices or the DDC should be described, where relevant.</p> <p>A comparison of the manufacturing process of DDCs from pivotal or bridging clinical studies to the commercial DDC should be presented, <i>where applicable</i>. Insert: Line 249 Where required (e.g. due to changes in device design during development), summary bridging data (see Section 7) should be provided in this section of the dossier, with cross-references to relevant data in Module 4 or Module 5, as appropriate.</p> <p>Appropriate data should be provided to demonstrate and justify the equivalence of the overall performance of the DDC prototype(s) used during pivotal clinical development with the DDC intended for marketing.</p>	The comment is acknowledged, however, the text is kept in P.2.2. in order to reflect all development not only manufacturing process development.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
426	L255-259	24	<p>Quote: A concise description of the DDC manufacturing process development...</p> <p><u>Comment:</u></p> <p>The scope for the documentation of the device part is unclear. Furthermore it may contain confidential information.</p> <p><u>Proposed change (if any):</u></p> <p>Please clarify.</p>	The comment is acknowledged, the text has been modified.
427	L260	14	<p><u>HIGH PRIORITY</u></p> <p><u>Comment:</u> The draft guidance proposes that the Manufacturing Process Development section describes the development of the DDC control strategy.</p> <p>It is requested that the guidance accommodates the use of risk-based approaches with elements of ICH Q8,9 and 10, as indicated by lines 241 – 242.</p> <p>To allow for flexibility, the guidance should allow providing information about the development of the control strategy for the integral DDC manufacturing process in section 3.2.R with a reference from P.2.3. to section 3.2.R.</p> <p><u>Proposed change (if any):</u> To add Risk-based approaches to assess impact of DDC quality attributes on quality, safety, efficacy and DDC functionality, using product-specific knowledge and prior knowledge from appropriately similar DDC products, is acceptable, as are conventional and hybrid approaches (ICH Q8, 9 and 10). The risk assessment may be developed to identify the DDC Critical Quality Attributes (CQAs). Reference may</p>	The comment is acknowledged, however, no update to the guideline is proposed. This is in line with the requirements for all other medicinal products.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			also be made to 3.2.R for description of the control strategy.	
428	L260	14	<p>Comment: "The development of the control strategy for the DDC manufacturing process should be described."</p> <p>It should be proposed something for legacy and well-established products.</p> <p>Proposed change (if any): For legacy/well established products, the suitability of the devices could be documented through retrospective analysis of data available from the end users (e.g. Pharmacovigilance, complaints, ...)</p>	The comment is acknowledged, however, no update to the guideline is proposed.
429	L260	9	Please clarify: if the final control strategy is reported in section 3.2.P.2.3 manufacturing process development, is it sufficient to cross-link to this part of M3 in section 3.2.P.3 (reference is made to EMA/CHMP/QWP/245074/2015)?	The comment is acknowledged. A general comment is included in the GL "To avoid repetition, it is acceptable to cross-reference between sections."
430	L261	9	There is a redundancy of information within P.2.4 and P.7. Suggestion is to be more specific on the difference between the two sections or to combine all Container Closure System information in P.7.	The comment is acknowledged, the text has been modified to focus on Development, interaction and performance in P.2 and description and control in P.7.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
431	L261	14	<p>Comment: This section should relate only to the container closure system and any device that is integral with; or forms part of the container closure system. Industry interpretation of container closure system is that part of the product which forms a closed container around the drug product.</p> <p>In the context of a pre-filled syringe (PFS), this can include a needle in some configurations (e.g. staked needle syringe), but not in others (e.g. luer-lock syringe, co-packed with injection needle). In a single use (disposable) autoinjector configuration, the autoinjector is integral with the container and thus is often included in this section for that reason.</p> <p>For a pressurised metered dose inhaler (pMDI) example, the actuator body is not part of the container closure system, however, it is often included in this section due to its integration with the canister.</p> <p>The wording of line 352/P7 is more specific and this should be replicated here.</p> <p>Proposed change: Clarify the expectations for inclusion of devices that are not fully integrated with the actual container closure system, into this section.</p>	The comment is acknowledged, however, no update to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
432	L261	19	<p>Comment: This section should relate only to the container closure system and any device that is integral with; or forms part of the container closure system. Industry interpretation of container closure system is that part of the product which forms a closed container around the drug product.</p> <p>In the context of a pre-filled syringe (PFS), this can include a needle in some configurations (e.g. staked needle syringe), but not in others (e.g. luer-lock syringe, co-packed with injection needle). In a single use (disposable) autoinjector configuration, the autoinjector is integral with the container and thus is often included in this section for that reason.</p> <p>For a pressurised metered dose inhaler (pMDI) example, the actuator body is not part of the container closure system, however, is often included in this section due to its integration with the canister.</p> <p>The wording of line 352/P7 is more specific and this should be replicated here.</p> <p>Proposed change (if any):</p> <p>Clarify the expectations for inclusion of devices that are not fully integrated with the actual container closure system, into this section.</p>	The comment is acknowledged, however, no update to the guideline is proposed.
433	L263, L276, L292, L420, L445 and L460	14, 19	<p>Comment:</p> <p>It is not clear whether EMA are suggesting these three headings should appear in the dossier.</p> <p>Proposed change (if any):</p>	The comment is acknowledged. It is not intended that these headings must appear in the dossier; however, if the applicant wishes to use these or other appropriate sub-headings as relevant, this is acceptable.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Clarify or change formatting of the guideline to avoid this potential confusion.	
434	L261-275	14	<p>Comment: The description and rationale section provides several bullets for device safety features that warrant at most “a brief description” however, the expansive bullets indicate unnecessary depth of description and in one bullet states “brief details”.</p> <p>Move text (line 247-248) from P.2.2 to P.2.4 and merge. It is not clear that it is acceptable to cross refer to relevant sections for the information, to avoid duplication.</p> <p>Proposed change: The following aspects of the development of the container closure system should be considered taking account of the risk management principles following ICH Q9 and/or EN ISO 14971 (refer to 3.2.R on the device constituent part):</p> <p><u>Description and rationale for DDC</u> A brief description of the container closure system should be considered with cross-references to relevant detailed data in 3.2.R if relevant and as appropriate, taking into account The applicant must take into consideration the intended use of the device and its suitability within the context of the DDC, its therapeutic indication and the relevant target patient population, including the rationale for the container and device component(s) and its (their) materials of construction, including, for example:</p>	<p>The comment is acknowledged.</p> <p>The guideline text has been amended and the bullet points modified. Section 4.1 of the updated guideline confirms that it is acceptable to cross-reference between sections of the dossier. It is not considered necessary to restate in this section. Risk management is mentioned earlier in the guideline and is considered an overarching principle, therefore reference is not repeated in this section of the guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> • Rationale for the container and device component(s) and its (their) materials of construction, <p>2. Line 271-272: Delete "Brief details" as contrary to line 264. "Brief details of Critical functional components e.g. power supply, dose-setting mechanism, description of controls and alarms and their instructions for use etc."</p> <p>3. Line 273: Delete "Brief description and rationale for" as this repeats line 264. "Brief description and rationale for any related technologies e.g. a software application."</p>	
435	L266	19	<p>Comment: Non-integral medical devices are not part of the container closure system and are discussed specifically in Section 6/536. It is confusing to include this bullet point here.</p> <p>Proposed change (if any): Remove this bullet point.</p>	<p>The comment is acknowledged. The guideline text has been amended to remove reference to non-integral medical devices.</p>
436	L266-268 and L271-273	28	<p>Comment: Should be removed, as this is not related to the container closure function (protect and hold the drug)</p>	<p>The comment is acknowledged. The guideline text has been amended to remove reference to non-integral medical devices and to reduce the examples of critical functional parts.</p>
437	L267-271	14	<p>Comment: Risk of confusion / duplication between "confirmatory signals" [267] and "critical functional components" [271]</p> <p>Proposed change (if any):</p>	<p>The comment is acknowledged. The guideline text has been amended to change to 'critical functional parts e.g. dose-setting mechanisms'.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Consider clarification of "critical functional components" in this context	
438	L267-268	27	<p>Comment: Sharps injury prevention features should be considered before and after using the device</p>	The comment is acknowledged. The current wording is considered to cover all sharps injury prevention features, and has been retained.
439	L269	26	<p>Comment: Line 269 describes the information to be provided in 3.2.P.2.4 section container closure system development for implantable/transdermal devices. However, according to the Guideline on quality of transdermal patches (EMA/CHMP/QWP/608924/2014), information on backing layers, liners and dressing are considered as excipients (please refer to paragraphs 4.2.3 Excipients, 4.2.8 container closure system and 4.4 control of excipients of the guideline EMA/CHMP/QWP/608924/2014). According to the guideline on transdermal patches, components of the device are considered as excipients and should be described in 3.2 P.4 section.</p> <p>Proposed change (if any): We would suggest to clarify which guideline should be followed and to modify/include a note regarding which guideline should be followed for device elements.</p>	The comment is acknowledged. This guideline refers to implantable/transdermal device (parts) rather than transdermal patches, and information on their development should be described in section P.2.4. The guideline is unchanged.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
440	L269-270	3	<p>Comment: It is not clear if medicated plaster (Ph. Eur. 04/2010:0132) and cutaneous patches (Ph. Eur. 04/2010:0132) according to definition in the European Pharmacopoeia are specified as integrals DDCs in this guideline. Only “transdermal devices” are mentioned in the guideline. It should be clearly defined which categories of patches/plasters are affected by this guideline. Please see also comment on 70 ff.</p> <p>Proposed change (if any):</p> <p>Add definition/explanation for “transdermal device” and/or add information about the other types of patches/plasters, if applicable.</p>	<p>The comment is acknowledged. This guideline refers to implantable/transdermal device (parts) rather than transdermal patches, and information on their development should be described in section P.2.4. The guideline is unchanged.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
441	L269-270	24	<p><i>Quote</i></p> <p>“For implantable/transdermal devices, information on the matrix and reservoir, including mechanism of drug release”.</p> <p><i>Comment</i></p> <p>The matrix and reservoir of the transdermal patch are not part of the container closure system. In compliance with the „Guideline on quality of transdermal patches“, these materials are clearly defined as excipients.</p> <p>Pouches are the container closure system of transdermal patches. The respective documentation and evaluation of the packaging material is provided in the CTD Module 3.2.P.2 and 3.2.P.7.</p> <p><i>Proposed change</i></p> <p>Please clarify what is meant with “implantable/transdermal devices”.</p> <p>Please delete second part of the sentence “information on the matrix and reservoir, including mechanism of drug release” in this section as these materials are not part of any container closure system.</p>	<p>The comment is acknowledged.</p> <p>This guideline refers to implantable/transdermal device (parts) rather than transdermal patches, and information on their development should be described in section P.2.4. The guideline is unchanged.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
442	L274-275	24	<p>Comment</p> <p>It is referenced to "Questions and Answers on EMA website", but the reference is not completely clear.</p> <p>Proposed change</p> <p>Please clarify.</p>	The comment is acknowledged. This reference is to the 'Quality of medicines Questions and Answers Part 2' on the EMA website. The guideline remains unchanged.
443	L274-275	23	<p>Comment</p> <p>We expect EMA to conduct a pro/con comparison of mg versus mL graduation scales, to determine which is better for preventing medication errors.</p>	The comment is acknowledged but is outside the scope of this guideline. No change is proposed.
444	L276	10	<p>Comment:</p> <p>Comply with the overarching requirements of a single location of files in eCTD structure and no duplication of information in different locations of the dossier.</p> <p>Proposed change:</p> <p>Delete the section "functional performance" and make a cross reference to section M3.2.R, where it should be located.</p>	<p>The comment is acknowledged.</p> <p>It is acknowledged that NBs may review this information, however a summary of this is expected in 3.2.P (from a medicinal product perspective), for ease of assessment.</p>
445	L276	14	<p>Comment:</p> <p>There exist standards for most device constituent parts of a DDC. We would suggest to state that sponsors should demonstrate conformance to standards when applicable rather than identify what should be included since the list is not exhaustive. In absence of an ISO standard, the sponsor</p>	<p>The comment is acknowledged.</p> <p>The guideline has been revised to indicate that conformance to relevant standards should be confirmed. Applicants are encouraged to seek SA if needed.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			should discuss with their Notified Body and Competent Authority (as necessary).	
446	L276-291	14	<p>Comment: Functional performance aspects per the intended use of the finished product (= integral DDC) will be subject for assessment by the NB, respective requirements are addressed under MDR Annex I (e.g. device must function as intended by the manufacturer). Therefore, this section should reference to the NB assessment report attached to section 3.2.R. In case EMA continues expecting this information in addition to the NB assessment report and to allow for flexibility, the guidance should allow providing this device related information in section 3.2.R with a reference from P.2.4. to section 3.2.R if needed.</p> <p>Proposed change (if any): This needs to be aligned about what is in/out of scope of NBOP vs. the CA requirements.</p>	<p>The comment is acknowledged.</p> <p>It is important for Assessors to see a summary of functional performance aspects in this section of the dossier in order to determine the appropriateness of the device with respect to aspects which may impact on the quality, safety and efficacy of the medicinal product. This will be assessed in conjunction with the NB assessment report in section 3.2.R. This requirement is retained in the guideline, which can only minimise duplication, not eliminate it.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
447	L276-291	27	<p>Comment: In the CHMP recommendation on Adrenaline Auto-Injectors adopted in 2015 (EMA/465403/2015), EMA states that "Several factors may affect whether adrenaline reaches the muscle layer. These include: needle length, the skin-to-muscle depth, the way the auto-injector works (e.g. if it is spring loaded or not), the angle of placement on the skin and the force used to activate the device". In light of a constantly increasing rate of obesity in children and adult populations in Europe, it seems to be necessary to consider functional performance of the devices in a holistic way, taking into account the above-listed factors.</p>	<p>The comment is acknowledged, and the guideline has been revised as follows:</p> <p><i>"Those factors that may impact the functional performance of the device should be discussed and considered in a holistic manner, e.g. posology, method of administration, physiological factors of the patient population, requirements in other EU guidelines, CHMP recommendations, etc."</i></p>
448	L277	14	<p>Comment: What does 'mechanical functionality' entail within the recommended P.2.4 section format.</p> <p>Proposed change: State that any mechanical functional testing on the device already reviewed under the Notified Body Opinion is not necessary to include for review under the MAA.</p>	<p>The comment is acknowledged.</p> <p>It is important for Assessors to see a summary of functional performance aspects in this section of the dossier in order to determine the appropriateness of the device with respect to aspects which may impact on the quality, safety and efficacy of the medicinal product. This will be assessed in conjunction with the NB assessment report in section 3.2.R. This requirement is retained in the guideline, which can only minimise duplication, not eliminate it.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
449	L277-279	14	<p>Comment: Edit for clarity.</p> <p>Proposed change (if any): Functional performance aspects of the DDC which impact quality, safety and/or efficacy should include dose accuracy and precision, mechanical 277 functionality and/or other functionalities directly related to the intended use of the device with the 278 medicinal product, such as dose accuracy, dose precision, and mechanical functionality and its impact on quality, safety and/or efficacy.</p>	<p>The comment is acknowledged; the guideline text has been amended to as follows. 'Functional performance aspects of the integral medicinal product should be limited to those aspects which impact quality, safety and/or efficacy (and hence overall benefit/risk determination) e.g. dose accuracy and precision over the range of (re)use, mechanical functionality and/or other aspects directly relevant to the intended use of the device (part) as part of the medicinal product'.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
450	L277-279	14	<p>Comment: Only critical functional performance aspects of the DDC should be described in any detail in P.2.4 Container Closure System. These would be CQAs as identified from the DDC risk assessment (see comments for lines 241-242). As such the guidance should be less prescriptive as more detailed device information will be provided as part of the Notified Body Opinion assessment process.</p> <p>Proposed change: "Functional performance aspects of the DDC should include those parameters considered critical for DDC product delivery, e.g. dose accuracy and precision, mechanical functionality and /or any other critical functionalities directly related to the intended use of the device with the medicinal product and its impact on quality, safety and/or efficacy, as determined through the DDC risk assessment."</p>	<p>The comment is acknowledged; the guideline text has been amended to as follows. 'Functional performance aspects of the integral medicinal product should be limited to those aspects which impact quality, safety and/or efficacy (and hence overall benefit/risk determination) e.g. dose accuracy and precision over the range of (re)use, mechanical functionality and/or other aspects directly relevant to the intended use of the device (part) as part of the medicinal product'.</p>
451	L277-278	21	<p>Comment: For some medical devices with variable dosers, it is the attending physician who decides the dosage and its variations, monitoring the administrations to the patients.</p>	<p>The comment is acknowledged; the guideline text has been amended to as follows. 'Functional performance aspects of the integral medicinal product should be limited to those aspects which impact quality, safety and/or efficacy (and hence overall benefit/risk determination) e.g. dose accuracy and precision over the range of (re)use, mechanical functionality and/or other aspects directly</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
				relevant to the intended use of the device (part) as part of the medicinal product'.
452	L278-279	28	<p>Comment: "Directly related to the intended use of the device with the medicinal product" – should be targeted even more towards the drug product as per the core precept of lines 155-157 (as it will otherwise impact all intended use)</p>	The comment is acknowledged; the guideline text has been amended to as follows. 'Functional performance aspects of the integral medicinal product should be limited to those aspects which impact quality, safety and/or efficacy (and hence overall benefit/risk determination) e.g. dose accuracy and precision over the range of (re)use, mechanical functionality and/or other aspects directly relevant to the intended use of the device (part) as part of the medicinal product'.
453	L280-281	14	<p>Comment: Edit for clarity.</p> <p>Proposed change: The ability of the device to deliver the medicinal product in accordance with the posology stated in Section 4.2 of the SmPC in an accurate and reproducible way should be demonstrated as per the posology stated in Section 4.2 of the SmPC.</p>	The comment is acknowledged; the guideline text has been amended as follows. ' The ability of the device (part) to deliver/ administer the medicinal product in accordance with the posology stated in section 4.2 of the SmPC in an accurate and reproducible manner should be demonstrated.
454	L283-285	14	<p>Comment:</p>	The comment is acknowledged; the guideline text has been revised as follows. ' As far as

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Concern test conditions to “simulate use of the DDC” – it could be clarified that this should not include simulation of interaction with the human body (e.g. injections into simulated tissue, etc.) which is difficult to simulate.</p> <p><u>Proposed change (if any):</u> Test conditions should, if appropriate, simulate the use of the DDC (e.g. dose delivery performance from an eye drop bottle should be evaluated from the dropper in various orientations) under relevant (in-use) storage conditions.</p>	possible, test conditions should simulate the use of the integral medicinal product under relevant (in-use) storage conditions. This need not necessarily include simulation of interaction with the human body.
455	L286-289	14	<p><u>Comment:</u> It is recommended to expand this requirement to clearly include considerations for post-shipping.</p>	The comment is acknowledged; the guideline text has been revised to include ‘where transportation studies are not presented in P.3.5, justification should be provided’.
456	L286-289	19	<p><u>Comment:</u> It is recommended to expand this requirement to clearly include considerations for post-shipping.</p>	The comment is acknowledged; the guideline text has been revised to include ‘where transportation studies are not presented in P.3.5, justification should be provided’.
457	L287	14	<p><u>Comment:</u> It is not appropriate to test all types of devices at beginning, middle and end therefore this should be as appropriate.</p> <p><u>Proposed change:</u> Consistency of dose delivery should be demonstrated through shelf-life as appropriate (e.g. beginning, middle and end for PFS)’ replace with ‘as appropriate’</p>	The comment is acknowledged, the guideline text has been revised to state ‘consistency of dosing (demonstrating that the medical device (part) accurately and precisely delivers the intended dose) should be guaranteed from release until the end of the shelf life and also during the use of the particular integral medicinal product under the conditions

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
				recommended in the SmPC (in-use stability testing)'. recommended in the SmPC (in-use stability testing)'.
458	L287-289	14	<p><u>Comment:</u> Clarity is requested on the expectation for 'precision and accuracy' through shelf-life. P.2.4 Container Closure System typically refers to P.8 Stability to demonstrate the suitability of the container closure system through shelf-life. Precision for delivered volume is demonstrated in the formal stability program through consistent data trend that is with the specified acceptance limits. Data or trends within the criteria would be considered as not meaningfully impactful of quality, safety or efficacy. Analytical precision within replicate data or between analysts etc. as well as accuracy are demonstrated by the validated method used and not repeated in stability testing through shelf-life.</p> <p><u>Proposed change:</u> "The precision and accuracy Consistency of dosing should be guaranteed from release until the end of shelf-life and also during the use of the particular DDC under the conditions recommended in the SmPC (in-use stability testing). Reference may be made to P.8 Stability"</p>	The comment is acknowledged; the guideline text has been revised to include 'consistency of dosing (demonstrating that the medical device (part) accurately and precisely delivers the intended dose) should be guaranteed from release until the end of the shelf life and also during the use of the particular integral medicinal product under the conditions recommended in the SmPC (in-use stability testing)'.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
459	L287-289	10	<p>Comment: Regarding precision and accuracy of dosing being guaranteed until end of shelf-life, it is suggested to clarify that this refers to data to be generated from on-going stability studies versus data required at the time of MAA submission.</p>	The comment is acknowledged; the guideline text has been revised to include 'consistency of dosing (demonstrating that the medical device (part) accurately and precisely delivers the intended dose) should be guaranteed from release until the end of the shelf life and also during the use of the particular integral medicinal product under the conditions recommended in the SmPC (in-use stability testing)'.
460	L288	20	<p>Comment: In order to avoid confusion, we recommend the following change.</p> <p>Proposed change (if any): Change "release until the end of shelf life" to "release until the end of the (in-use) shelf life."</p>	The comment is acknowledged; the guideline text has been revised to include 'consistency of dosing (demonstrating that the medical device (part) accurately and precisely delivers the intended dose) should be guaranteed from release until the end of the shelf life and also during the use of the particular integral medicinal product under the conditions recommended in the SmPC (in-use stability testing)'.
461	L290	23	<p>Comment: In order to prevent such issues, EMA must require marketing authorisation or variation applicants to conduct user testing by target patient groups or health professionals, including tests to determine the risk of usage errors.</p>	The comment is acknowledged; the guideline has been revised to state 'the effects of simulated real-world in-use conditions should be discussed, and data provided as appropriate e.g. shaking, priming, dropping test'.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
462	L291	14	<p>Comment: We suggest to remove Human Factors in parenthesis after Usability Studies and add including HF Studies or change to Usability data or Usability Engineering. Human Factors studies which are utilized to gather usability data. Further, a DDC may require a Usability Study, e.g., clinical gathering real world use information in addition to human factors validation study.</p> <p>Proposed change: For usability tests (including human factor studies) studies, see 3.2.R (Section 5.4, below).</p>	The comment is acknowledged; the guideline text has been revised to remove reference to (human factors).
463	L292	14	<p>Comment: Suggest including that for products which include a diluent in DDC for reconstitution, the diluent compatibility with the device part should also be addressed by the sponsor</p>	The comment is acknowledged; the guideline text has been revised to include any diluents for reconstitution.
464	L292	2	<p>“Compatibility” Comment: There are 2 important issues to be considered;</p> <ul style="list-style-type: none"> - First instructions on how to clean reusable inhalers (one GP explained she had to make a booklet to distribute to her patients in a rural practice) as there was nothing available. - Second, allergies to some parts of the inhaler are never mentioned e.g. allergy to latex <p>Proposed change:</p>	The comment is acknowledged. The guideline text has been revised (Section 5.1 and Section 6.1.1)

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Provide clear instruction on how to clean the inhaler	
465	L292-309	14	<p>Comment: Why is compatibility discussed in P.2.4 and not in P.2.6, which is specifically dedicated to compatibility discussion?</p> <p>Proposed change: Move compatibility discussion to P2.6</p>	The comment is acknowledged, the guideline text has been revised to move compatibility to section P.2.6.
466	L292-309	14	<p>Comment: As the intended use of the integral DDC is related to a specific drug product, respective compatibility between device and drug is required by MDR Annex I section 10.ff, in particular in section 10.3. The NB would review in most parts the same evidence of compliance as required by this guidance to include in section P.2.4 of the MAA. It seems redundant that both the NB and the medicines agency review the same information. Please outline in greater detail, if e.g. 10.3 should not be reviewed for an integral DDC by a NB in case this information is provided in the MAA Section P.2.4., and is reviewed by the medicines agency in order to avoid redundant review.</p>	<p>The comment is acknowledged.</p> <p>The Competent Authority is responsible for assessing the dossier with reference to EU legislation, guidelines and other relevant documents, taking into account current scientific knowledge and understanding. NBs have different legal obligations and focus. This requirement is therefore retained in the guideline, which can only minimise duplication, not eliminate it.</p>
467	L293-307	6	<p>Comment: The guidance provided here is correct but since this is fully in line with general guidance for container closures and in-use stability of medicinal products it can be covered by reference to existing guidance.</p>	The comment is acknowledged. Reference to applicability of other guidelines is included in Section 3.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
468	L295	5	<p>Comment: Who would evaluate drug/ device interactions? NBOP or CA review or both. See comment L155.</p>	<p>The comment is acknowledged.</p> <p>Drug-device interactions are within the remit of the CA whereas device-drug interactions are within the remit of the NB.</p>
469	L295-299	14	<p>Comment: This paragraph discusses the compatibility between device and drug product with respect to the physical and chemical aspects. It states: <i>“Interaction studies, including extractable and leachable studies as appropriate, should be performed.”</i> It is not clear what an interaction study entails and when extractables and leachables (E&L) studies are appropriate. The device is subject to biocompatibility testing as described in ISO 10993 series which includes Part 17 “Establishment of allowable limits on leachable substances” and Part 18 “Chemical characterization of materials”. Please provide details on when ISO 10993-17 and ISO 10993-18 may be appropriate for the device as well as the DDC.</p> <p>Proposed change: “The physical and chemical compatibility of the drug product with the device(s) should be demonstrated. All materials in contact with the drug product should be considered. Interaction studies, including extractable and leachable studies as appropriate, should be performed. These should include physical and chemical compatibility (e.g. sorption,</p>	<p>The comment is acknowledged; the guideline text has been amended. Reference to specific ISO standards has not been included.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			precipitation of drug substance in solution, and stability, etc.). The device should be evaluated for biocompatibility testing standards as appropriate (e.g. ISO 10993). Extractable and leachable (E&L) studies should demonstrate that E&L substances from the devices do not impact the safety, efficacy and quality of the medicinal product."	
470	L296	14	Comment: Drug product contacting materials, may be container closure and fluid path. Suggest, after drug product, insert drug container and fluid path	The comment is acknowledged; the guideline text has been amended.
471	L297	8	Comment: The documentation, considerations and studies according EN ISO 10993-17:2009 "Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances" contain such information. We recommend that the acceptance of data collected according this standard is supported by this draft guideline so far the data are transferrable to the particular intended use of the device in combination with the particular pharmaceutical product in question.	The comment is acknowledged; the guideline text has been amended. Reference to specific ISO standards has not been included.
472	L301	14	Comment: We would suggest here a step by step approach: first risk assessment based on supplier data (extractable, material safety datasheet and NOAEL of each extractable component) and based on the risk assessment outcomes, initiate the leachables to ensure that in real conditions of use the devices present no risk. BUT NO leachable studies upfront.	The comment is acknowledged. The guideline does not explicitly exclude the use of a risk-based approach; the use of a specific approach should be justified on a case-by-case basis. Therefore, no change is made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
473	L301 and L300-302	14	<p>Comment: Text mentions that a leachable study should be performed to evaluate the effect of their effects of the drug product. However, a leachable study may not be the most appropriate approach to evaluate any potential effect of leachables on the drug product. Moreover, for an integral DDC, there is no need to perform a compatibility study, except for exploratory reasons.</p> <p>The above comments are justified as follows: the integral DDC will anyway need to be tested (including for drug product quality attributes) at real-time time intervals per ICH Q1A and Q5C (for biologics), and data provided in P.8. These stability data will give evidence on whether leachables have or not an impact on the drug product during long-term storage, and will show whether the device and drug product are compatible or not.</p>	The comment is acknowledged; the guideline text has been amended.
474	L306-307	22	<p>Comment: The language 'under different orientations' is too general and may lead to unnecessary testing. PDA suggests that the 'worst-case orientation' is more appropriate.</p> <p>Proposed change: Under different worst-case orientations...</p>	The comment is acknowledged; the guideline text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
475	L309	11	<p>Proposed change (if any): After this comprehensive description of container closure system requested information, add: It is acknowledged that the Drug Product Manufacturer may be able to leverage elements of the Device Manufacturer’s design controls to document this module. The information leveraged should be agreed upon between the two parties defining maintenance and sharing of design information.</p>	<p>The comment is acknowledged.</p> <p>The proposed text is outside of scope of this guideline. No change to the guideline is proposed.</p>
476	L310	5	<p>It would be useful if this guidance could clarify who will review these data. For example, sterility is related to device aspects but the NB are not reviewing the QMS. Do we perform a desktop review of sterilisation validation or can we be assured this can be left to the Competent Authority?</p>	<p>The comment is acknowledged. The definition of NB activities pertaining to sterile devices is outside the scope of this guideline. No change to the guideline is proposed.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
477	L311-312	14	<p>Comment: Section 3.2.P.2.5 typically qualifies the proposed container closure system for integrity. Although some companies use container closure integrity (CCI) testing in place of Sterility in the stability testing program, this should not now be mandated. The Sponsor should have the option to justify the container closure system qualification is sufficient. The need for DDC CCI testing should be risk-based. Assembly of a DDC is usually assessed as low risk manufacture since the risk of compromising CCI in a well-designed and control process is very low. Indeed, it is understood that the agency and Inspectorate consider assembly as 'functional secondary packaging'.</p> <p>Proposed change: For sterile products, the integrity of the DDC throughout use and shelf-life, as it relates to preventing microbial contamination should be demonstrated. Integrity of the container closure system through use and shelf-life should be considered using risk-based principles."</p>	The comment is acknowledged; however the guideline does not mandate a specific approach to demonstrate integrity. No change to the guideline is proposed.
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.3 – MANUFACTURE (L313-340)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
478	L313	19	<p>Comment: Given that it is not discussed in section 6, it would be useful to clarify the expectations for manufacturer and manufacturing information related to non-integral products versus integral products. For co-packaged products incorporating CE-marked devices, the manufacturing information related to the device should not be necessary in the dossier, on the basis that it has been reviewed as part of conformity assessment of the device.</p> <p>Proposed change (if any): Create separate considerations for manufacturing information for integral vs non-integral.</p>	The comment is acknowledged; the information in this section relates to the drug product manufacturer(s). The guideline has been revised to clarify that 'suppliers of the device (part) and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section'.
479	L314-316	24	<p><i>Comment</i></p> <p>What is meant by manufacturer for "DDC assembly"? Manufacturers listed in 3.2.P.3.1 are typically expected to be GMP-certified which will not be the case for any facility involved in the preparation or pre-assembly of a device prior to medicinal product manufacture. According CTD guidance, manufacturers of primary packaging are not foreseen to be given in section P.3.1.</p> <p><i>Proposed change</i></p> <p>Delete lines 314 to 316</p>	The comment is acknowledged; the guideline text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
480	L315	19	<p>Comment: Device constituents of integrated products are often provided by the supplier as 'sub-assemblies' to permit straightforward final assembly steps of the device around the drug product. Therefore, the reference here to manufacturer details for DDC assembly would benefit from clarification.</p> <p>Proposed change (if any): Clarify expectations for device sub-assembler information.</p>	The comment is acknowledged; the information in this section relates to the drug product manufacturer(s). The guideline has been revised to clarify that 'suppliers of the device (part) and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section'.
481	L315-316	9	Please clarify: if a sub-assembly operation for the device constituent is performed by a partner/contractor, should this third party be also listed in section 3.2.P.3.1 as manufacturers? (Compare also to Lines 322-325, allowing the reference to be included in section P.7 instead).	The comment is acknowledged; the information in this section relates to the drug product manufacturer(s). The guideline has been revised to clarify that 'suppliers of the device (part) and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section'.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
482	L315-316	14	<p>Comment: The DDC assembly, sterilisation etc sites are requested in P.3.1 but this may not always be appropriate. Manufacture of a PFS is already provided under the current guidance for a medicinal product with any assembly accepted as 'functional' secondary packaging. Concerning sterilisation, most aseptically filled biologics would not tolerate sterilisation.</p> <p>Clarity is requested when DDC manufacturer sites and sterilisation sites are considered appropriate in P.3.1.</p> <p>Proposed change: In addition to the proposed clarification: "As appropriate, manufacturer names/addresses for DDC assembly, packaging, DDC sterilisation labelling and quality control sites, as well as for the EU batch release site(s) should be stated."</p>	The comment is acknowledged; the information in this section relates to the drug product manufacturer(s). The guideline has been revised to clarify that 'suppliers of the device (part) and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section'.
483	L317	14	<p>Comment: Devices in integral DDCs are typically not the finished product, rather a component, which is filled (for a PFS the device is the primary container) and assembled, labelled and packaged to result in the finished integral DDC product.</p> <p>For the finished product (= integral DDC) the assembly, labelling and packaging process will be subject to assessment by the NB as Annex I MDR has respective requirements (Annex I Chapter II "design and manufacture", e.g. section 10 ff.).</p> <p>To avoid that the NB and the medicines agency review the same information, it should be clearly indicated by EMA if the filling, assembly, labelling and packaging process of the finished product should be also assessed by the NB as</p>	The comment is acknowledged; The Competent Authority is responsible for assessing the dossier with reference to EU legislation, guidelines and other relevant documents, taking into account current scientific knowledge and understanding. NBs have different legal obligations and focus. This requirement is therefore retained in the guideline, which can only minimise duplication, not eliminate it

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			detailed information will be provided in Sections P.3 of the MAA dossier. Please also refer to general comment.	
484	L318-320 and L378-379	23	Although beyond the aims of this draft guideline, drug regulatory agencies also need to address the issue of the stability of medicinal products when not protected by their primary packaging, in particular for the purposes of automated dose dispensing.	The comment is acknowledged; however, this is out of scope of the guideline. No change to the guideline is proposed.
485	L322	22	<p>Comment: PDA believes that, when EMA uses the term 'DDC manufacturer' in this discussion of Integral DDCs, EMA intends to refer only to the pharmaceutical company or the CMO/CDMO that combines the drug and the device into a DDC. It does not refer to the manufacturer of the medicinal product or of the medical device, unless that manufacturer also combines the two items into an integral DDC. This understanding appears to be supported by the language in lines 328-329.</p> <p>Proposed change: PDA suggests that EMA consider clarifying this language, especially if PDA's interpretation is incorrect.</p>	The comment is acknowledged; the information in this section relates to the drug product manufacturer(s). The guideline has been revised to clarify that 'suppliers of the device (part) and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section'.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
486	L322	28	<p>Comment: It is not in the interest of EMA or the public to freeze device design this way. "Description of any operations..." can be accomplished; however, without any EMA guidance on change control, which will limit the opportunity for continuous improvement for the benefit of patients and could overload Agencies with non-significant changes.</p> <p>Proposed change (if any): Edit to read: "Description of any operations that are performed on the device(s) by the DDC manufacturer, insofar it is judged to influence DDC safety or performance (such as subassembly steps, ...)"</p>	The comment is acknowledged; the guideline text has been amended accordingly.
487	L322-323	14	<p>Comment: Clarification is requested on the DDC manufacturer since the list of example operations includes 'subassembly steps'. A description of subassembly manufacture should not be considered required in the drug CTD sections and resides in the NBOp. The third bullet covers the final assembly.</p> <p>Furthermore, the level of detail can vary from device to device therefore the level of detail should be in relation to the device.</p> <p>Proposed change: "Appropriate description of any operations that are performed on the device component(s) by the DDC manufacturer to prepare subassembly components ready for final assembly of the DDC (such as subassembly steps, washing, coating, sterilisation, or depyrogenation etc.)."</p>	The comment is acknowledged; the guideline text has been amended accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
488	L322-325	10	<p>Comment: It is not clear what type of information (lines 323 and 324) on the sites performing the operations described in lines 322 and 323 is requested that would be in addition to the information already included in P.3.1.</p> <p>Proposed change: Including definitions to differentiate the manufacturer for DDC assembly mentioned in line 315 and the DDC manufacturer mentioned in line 322, or providing more specific details about the type of manufacturer site information that is expected to be included in P.3.3 may improve clarity of this section.</p>	The comment is acknowledged; the guideline text has been amended accordingly.
489	L323	2	<p>“Coating” Comment: For example, aero chambers need to be cleaned regularly. However, some patients use hot water with a lot of soap and scratch the inside which will damage the aero chamber.</p> <p>Proposed change Clear information about cleaning the inhaler needs to be provided. Preferably with pictures.</p>	The comment is acknowledged. This relates to patient use rather than manufacture. Cleaning of the device is mentioned in Section 5.2 of the amended guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
490	L323-325	14	<p>Comment: Information about manufacturing sites for the DDC is provided in P.3.1 Manufacturers. No need to repeat.</p> <p>Proposed change: Delete the following: Information on the sites performing these steps could be presented in this section of the dossier or reference given to section P.7.</p>	The comment is acknowledged; the guideline text has been amended accordingly.
491	L326-327	14, 31	<p>Comment: The guidance requests a description of the DDC sterilisation methods and conditions (where relevant) and suggests validation method may need to be described or requested. However, for many syringe filling methods using aseptic processes, pre-sterilised syringe barrels are typically obtained, and drug product sterility is a release test. The final assembly for pre-filled pens does not present a significant risk to the drug and sterility is not required above aseptic processing.</p> <p>Proposed changes:</p> <ol style="list-style-type: none"> 1. Additional guidance should be provided to clarify when this requirement is relevant. 2. Replace line 327: "The sterilisation method (s) should be validated. <p>Information on sterilisation of device components should be presented in this section of the dossier or reference given to another appropriate section."</p>	The comment is acknowledged; the guideline text has been amended accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
492	L328-330	14	<p>Comment: Acceptance criteria for critical controls are presented in P.3.4 typically, as per ICH M4Q. This section should list parameters indicating those that are critical.</p> <p>Proposed change: A description of the filling steps and the final assembly of the device(s) into the DDC, as performed by the DDC manufacturer should be detailed together with critical process parameters <u>and</u> in-process controls and acceptance criteria (for critical steps).</p>	The comment is acknowledged; the guideline text has been amended accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
493	L331	14	<p>HIGH PRIORITY</p> <p>Comment: Label may be applied to the device rather than to the container. An example would be when a pre-filled syringe (i.e. the container) is not labelled, and instead a product label is applied to the surrounding autoinjector or pen component.</p> <p>In either case, the Sponsor should have the flexibility to employ risk assessment to determine critical IPCs. Critical quality attributes and their control would be part of the overall control strategy. Label position as a critical IPC would be specific to a particular DDC where a label may have a measuring function or other critical purpose.</p> <p>Proposed change: “For applied labels which include printed markings, the position of the label on the container should 332 be specified and acceptable tolerances for the label positioning defined as critical in process controls 333 (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4. Applied labels with a functional role should be described and, when applicable and assessed as critical, with acceptable tolerances for label positioning.”</p>	<p>The comment is acknowledged; the guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
494	L331	17	<p>Comment: The term “printed markings” can have multiple definitions depending on the context of its use including, but not limited to, CE marks and dose indicators. To better guide Sponsors regarding applied labels, we request that Agency clarify what specifically is meant by “printed markings”.</p> <p>Proposed change (if any): None</p>	The comment is acknowledged; the guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.
495	L331	19	<p>Comment: Label may be applied to the device rather than to the container. An example would be when a pre-filled syringe (i.e. the container) is not labelled, and instead a product label is applied to the surrounding autoinjector.</p> <p>Proposed change (if any): Also, state expectations for when the label is not placed on the container; but on the device instead.</p>	The comment is acknowledged; the guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.
496	L331-333	10	It’s unclear to what/why labeling positioning would need an associated IPC	The comment is acknowledged; the guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.
497	L331-333	23	Avoid markings/graduations printed on a label. Embossed markings/graduations are preferable.	The comment is acknowledged; the guideline text has been amended as follows: ‘Applied labels with a functional role should be

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
				described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.
498	L331-333	27	<p>Comment: EMA should also take into consideration other labelling technicalities such as font size, letter emphasis etc.</p> <p>Proposed change (if any): For applied labels which include printed markings, the position of the label on the container should be specified and acceptable tolerances for the label positioning defined as critical in-process controls (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4. Moreover, rules for other labelling technicalities, including on font size and letter emphasis, should be defined.</p>	The comment is acknowledged; however, the proposed wording is relevant for all medicinal products, not just DDCs. The guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.
499	L331-333	31	<p>Comment: For applied labels which include printed markings, the position of the label on the container should be specified and acceptable tolerances for the label positioning defined as critical in-process controls (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4.</p> <p>Proposed change: We recommend this section to be in either module 1 or in 3.2.P.7</p>	The comment is acknowledged and control of applied labels would be expected if performed as part of manufacture. The guideline text has been amended as follows: ‘Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined’.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
500	L335	14	<p>Comment: The term 'device-specific intermediates' is assumed to refer to manufacture of sub-assemblies, however this assumption may not be correct. Please clarify examples of device-specific intermediates since the information requested here seems to overlap with the P.7 subsection below, which indicates that specifications for devices and/or device components be included in P.7. It may be helpful to cross refer to the P.7 section for expected information when the device components are part of the container closure system.</p> <p>Proposed change (if any): Provide definition and provide examples.</p>	The comment is acknowledged. The guideline text has been amended as follows: 'any device (part) specific intermediates (sub-assemblies) produced during manufacture of the integral medicinal product).
501	L335	19	<p>Comment: The term 'device-specific intermediates' is not defined. This is assumed to refer to sub-assemblies, however this may not be correct.</p> <p>Proposed change (if any): Provide definition.</p>	The comment is acknowledged. The guideline text has been amended as follows: 'any device (part) specific intermediates (sub-assemblies) produced during manufacture of the integral medicinal product).
502	L335-336	31	<p>Comment: Any critical steps should be justified, and any device-specific intermediates should be defined, along with relevant specifications, test methods and their validation. Any holding times should be defined and justified.</p> <p>Proposed change: Add an example for Device specific intermediates</p>	The comment is acknowledged. The guideline text has been amended as follows: 'any device (part) specific intermediates (sub-assemblies) produced during manufacture of the integral medicinal product).

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
503	L335-337	14	<p>Comment: Clarification is proposed to link 'critical steps' with critical parameters and controls</p> <p>Proposed change: Any critical steps should be justified, and critical process parameters and in-process controls for manufacture of the DDC should be provided along with acceptance criteria. and any any device-specific intermediates should be defined, along with relevant specifications, test methods and their validation.</p> <p>Any holding times should be defined and justified.</p>	The comment is acknowledged; the guideline text has been amended accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
504	L338-340	14	<p>HIGH PRIORITY</p> <p>Comment: Most of the DDC manufacturing process will fit in the scope of 'Non-standard' manufacturing process EMA guidance EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1, Corr.1. It will be beneficial to understand if full-scale batch data would be required for Process validation for every DDC or a risk-based approach may be used.</p> <p>DDC assembly under controlled conditions, when the process presents low risk to the integrity of the prefilled container closure system (discussed in P.2.5) and considered as standard process, should allow validation to be concurrent with the MA review with an outline of the assembly validation procedure laid out in P.3.5 (see EBE reflection paper on <i>Medicinal product incorporating a drug delivery device component: An industry Perspective on developing an Efficient, 'End to End' Control Strategy</i>, 12 June 2019.</p> <p>Proposed change: Add at end of line 340: "When assembly of drug with device components is justified to be of low risk, a supporting summary of the PPQ approach may be provided with cross-reference to 3.2.R. Assembly process validation should be completed prior to launch of the DDC product."</p>	The comment is acknowledged; however, guidance is already provided in the EU process validation guideline. No change to the guideline is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
505	L340	28	<p>Comment: P.3.5 Process validation and/or evaluation can be interpreted as a requirement to validate manual assembly processes.</p> <p>Proposed change (if any): Edit to read: Process validation for the manufacture of the DDC should be performed in line with relevant European guidelines, where outcome of the process cannot be adequately verified by inspection, including the assembly...</p>	The comment is acknowledged. The guideline text has been amended accordingly.
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.5 – CONTROL OF DRUG PRODUCT (L341-351)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
506	L342-351	14	<p>HIGH PRIORITY</p> <p>Comment: Whilst intent appears clear, the difference between performance tests and other critical parameters is open to significant interpretation, particularly when considering the examples given.</p> <p>There are concerns about including this number and level of testing in the Specifications section. Wording that relates to risk-based control strategy would be beneficial.</p> <p>A risk-based approach to DDC control strategy and identification of CQAs for end-product release testing is proposed. While a conventional control strategy would employ end-product (= integral DDC) release testing for all CQAs, it is possible to move many product attributes, that are conventionally controlled by release testing against the specifications, to upstream manufacturing in-process controls when a risk-based Product Quality Risk Assessment, or equivalent, is applied.</p> <p>Indeed, when supported by data, including Prior Knowledge, the risk associated with low attributes is low enough that they can be removed from routine control (non-routine control such as for product comparability exercises or at process validation is still recommended).</p> <p>Please refer for more information to the EBE Reflection Paper published on 12 June 2019:</p> <p>EBE Reflection Paper: Medicinal product incorporating a drug delivery device component: An Industry Perspective on developing an efficient, 'End to End' Control Strategy</p>	<p>The comment is acknowledged. The non-exhaustive list of examples has been retained. The guideline text has been amended accordingly to specify 'other critical test parameters related to CQAs of the integral medicinal product where earlier controls are not in place'.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>It is requested that the guidance is less prescriptive (even though perhaps unintentional). Furthermore, extractable volume and delivered dose uniformity should be alternative tests as only one is required.</p> <p>Proposed change: Provide further clarity on how this section should be interpreted.</p> <p>“The DDC specification should include those parameters that have been identified as CQAs of the medicinal product and that are controlled on the finished product. If DDC controls are in place prior to the finished product these should be specified in the relevant sections (e.g. P3.3, P3.4, P.7).</p> <p>When appropriate, the specification should include the following:</p> <ul style="list-style-type: none"> • Description of DDC appearance • Critical performance tests relevant to the intended use of the DDC e.g. extractable volume, or delivered dose uniformity and any functionality of the device at both release and shelf-life. • Performance of the DDC at release and shelf-life should be addressed.” 	
507	L343	6	<p>The term ‘appropriate’ is too vague.</p> <p>Proposed change (if any): A clear link with development can be made (in line with ICH Q8/9/10), as applicant’s can state in development if certain parameters do not have to be included in the specification.</p>	<p>The comment is acknowledged. The guideline text has been amended accordingly to state that ‘the specification should include those parameters that have been identified as CQAs of the medicinal product and that are controlled in the integral medicinal product’.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
508	L344	28	Comment: Remove, as this is irrelevant for the drug product as per core precept of lines 155-157	The comment is acknowledged. No change to the guideline is proposed.
509	L345	22	Comment: 'Extractable volume' is not frequently used, and therefore may not be clear to many users. We believe that EMA means to refer to the drug volume being expelled by the device, and we recommend that EMA use those words specifically. Proposed change: ... extractable -volume expelled by the device	The comment is acknowledged. No change to the guideline is proposed. Extractable volume is a commonly used term in marketing authorisation applications and in the European Pharmacopoeia.
510	L347	35	With reference to the Critical Quality Attributes (CQAs), it is not clear if they are referred to the medicinal product itself or to the drug-device combination. Please clarify.	The comment is acknowledged. The guideline text has been amended accordingly
511	L347-351	10	A majority of the CQAs provided as examples may be fixed parameters in the DDC design (needle length) or IPCs (seal integrity). We recommend that this be considered for deleted from specification section as these attributes may not be a function of product quality and are more a function of design of the DDC.	The comment is acknowledged. The non-exhaustive list of examples has been retained. The guideline text has been amended accordingly to specify 'other critical test parameters related to CQAs of the integral medicinal product where earlier controls are not in place'.
512	L347-351	14	<u>HIGH PRIORITY</u> Comment: There are concerns about including this number and level of testing in the Specs section, which is typically reserved for IPC and release testing. Furthermore, some tests are listed that are often considered as alternatives (e.g.	The comment is acknowledged. The non-exhaustive list of examples has been retained. The guideline text has been amended accordingly to specify 'other critical test parameters related to CQAs of the integral

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>extractable volume or delivered dose uniformity). These concerns warrant further clarification.</p> <p>Most performance tests are typically not added to the final specification for batch release since controls and checks could be placed at points in the process where checks are more effective. This is in line with ICHQ 8, 9 and 10. Syringe tests parameters such as glide force, activation force and needle penetration force are usually considered as not required to be tested routinely on final containers, hence location in 3.2.P.5.1 does not seem to be appropriate. Should instead be described in 3.2.P.2.4 or 3.2.R as part of the design verification studies or P.7 in case performed as a release test on the device part. Furthermore, specific functionality parameters are assessed by the NB. There is significant concern that this list could become expected CQAs for routine testing.</p> <p>Proposed change: Delete all but start of paragraph.</p> <p>Any other non-performance, critical test parameters related to identified as CQAs of the medicinal DDC product. e.g. glide force, needle penetration force, seal integrity, delivery time, exposed needle length after activation of device (needle penetration depth, relevant to route of administration), activation force, transdermal adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose delivery to the patient/user."</p>	<p>medicinal product where earlier controls are not in place'.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
513	L349-350	24	<p><i>Quote</i></p> <p>Other critical test parameters related to CQAs of the medicinal product, e.g. glide force, needle penetration force, seal integrity, delivery time, exposed needle length after activation of device (needle penetration depth, relevant to route of administration), activation force, transdermal adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose delivery to the patient/user.</p> <p><i>Comment</i></p> <p>Following the requirement of the „Guideline on quality of transdermal patches“ adhesion properties test are part of the development of transdermal patches. The respective information is already provided in the CTD. Also adhesion properties, such as adhesion force and peel force, are specified in the medicinal product specification (3.2.P.5.1).</p> <p><i>Proposed change</i></p> <p>To avoid double regulation, we propose to amend this section and to delete the example “transdermal adhesion properties”.</p>	The comment is acknowledged. The wording relating to transdermal adhesion properties is not included as this overlaps with existing guidance. No change to the guideline text is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
514	L351	14	<p>Comment: Sections P.5.2 Analytical procedures, P.5.3 Validation of analytical procedures, P.5.4 Batch analysis, P.5.6 Justification of specifications are missing.</p> <p>Proposed change: Add as option to use the sections mentioned, or cross reference in P.5 to other sections such as 3.2.R or NBOp</p>	The comment is acknowledged. These sections are not included because no additional guidance for these sections is required. An additional sentence has been added to Section 4.2 of the guideline for clarification.
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.7 – CONTAINER CLOSURE SYSTEM (L352-368)</u>				
515	L352	19	<p>Comment: Refer to comments to 261, above</p>	The comment is acknowledged. No change to the guideline is proposed.
516	L352-368	3	<p>Comment: No reference is made to the need to mention the manufacturer/supplier of the device.</p>	The comment is acknowledged. The guideline text has been revised as follows: 'specifications should reflect the complexity of the medical device and or device constituent(s), such that equivalence between suppliers can be assured. Unless justified, the supplier of device (part) should be defined in this section'.
517	L353-354	14	<p>Comment: This section should relate only to any device component that is integral with; or forms part of the container closure system. Industry interpretation of container closure system is that part of the product which forms a closed container around the drug product – primary packaging.</p> <p>In the context of a pre-filled syringe (PFS), this can include a needle in some configurations (e.g. staked needle syringe), but not in others (e.g. luer-lock syringe, co-packed with</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>injection needle). In a single use (disposable) autoinjector or pen configuration, the autoinjector or pen is integral with the container and thus is often included in this section as functional secondary packaging.</p> <p>For a pressurised metered dose inhaler (pMDI) example, the actuator body is not part of the container closure system, however, is often included in this section due to its integration with the canister.</p> <p>This section introducing term of primary packaging in addition to device component. This may be confusing when considering a prefilled pen may include a prefilled syringe within a pen.</p> <p>As written, it is not clear which component may constitute primary packaging and which is the device.</p> <p>Suggest consistency and definition of primary packaging be provided.</p> <p>Proposed changes:</p> <ol style="list-style-type: none"> 1. Definition of 'Primary Packaging'. 2. "Where the device is part of the primary container closure system (immediate packaging) as intended for marketing (e.g. staked in needle) or forms part of the functional secondary packaging (e.g. pen subassemblies enclosing a PFS), the following information should be provided:" 	
518	L355-356	14	<p>Comment: Clarification needed on the expectations for a device specification in the context of a DDC product.</p> <p>The primary packaging components specification should be included or cross-referred. The device components should</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>only require compliance to the applicable ISO standards that may be cross-referred e.g. in 3.2.R.</p> <p>This text appears to overlap with lines 362 and or 368, requesting device specification and compendial standards. Deletion is requested to avoid confusion over the multiple references to specification in this section.</p> <p>Proposed change: "A description of the container closure system, including materials of construction of each primary packaging and secondary packaging device component and its specification."</p>	
519	L355-356	26	<p>Comment: according to the present guideline, a description of the container closure system, including the materials of construction of each primary packaging and device components and its specification should be provided in section P.7 container closure system (lines 355-356). This is not aligned with the guideline on transdermal patches where information on device components should be described in 3.2 P.4 section.</p> <p>Proposed change (if any): We would suggest to clarify which guideline should be followed and to modify/include a note regarding which guideline should be followed for device elements.</p>	<p>The comment is acknowledged. The guideline text has been amended accordingly.</p> <p>Where device components are defined as excipients they should be described in P.4, otherwise components should be described in P.7 (with reference to information in 3.2.R as necessary).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
520	L355-356 and L363-L366	10, 24	<p>Comment: The Notice to Applicants Volume 2B describes the information to be given regarding the container closure as follows: <i>"A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided."</i></p> <p>Proposed change: According to these rules, technical drawings and photographs are not part of the module P.7 (only where appropriate). This information (technical drawings and photographs) should not mandatorily be part of the module P.7.</p> <p><i>Proposed change</i> To avoid double regulation, delete this section.</p>	The comment is acknowledged. The wording of the guideline has been revised with reference to the Notice to Applicants.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
521	L356	28	<p>Comment: Remove last part: “and device component and its specification”, as this should be limited to primary packaging (rest of device materials are covered in device GSPR’s) – otherwise a simple device change can trigger a drug variation – very ineffective and not adding value.</p>	The comment is acknowledged. The guideline text has been amended accordingly
522	L357-361	14	<p>Comment: Information about manufacturing sites for the DDC is provided in P.3.1 Manufacturers. No need to repeat here.</p> <p>In addition, propose to keep all information on any sterilisation in P.3.3 and prevent duplication in P.7 (this is in line with non-device drugs).</p> <p>Can the last statement, on using a CE-marked device, be valid for drug-device integral products where the device is not CE marked? Since as per article 117, NB opinion will assess the compliance with GPSRs from MDR Annex 1 (which includes sterility assessment as per SPR 11.4: Devices delivered sterile)</p> <p>Proposed change: Delete first sentence 357-358 and move the remainder to 3.2.P.3.3: Information on sites and processes for sterilisation and/or subassembly of device(s), or reference to section P.3. Move lines 358 – 361 to section P.3.3 under line 327: “When empty, sterile, ready-to-use container closure components are purchased, information should be provided</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			in line with the EMA Sterilisation guideline (EMA/CHMP/CVMP/QWP/BWP/850374/2015). Where a sterile CE-marked device is used, the inclusion of the NB Certificate of Conformity is sufficient to demonstrate sterility.”	
523	L357-361	24	<i>Comment</i> Information on compliance with sterilisation guideline may not be available to the MAH. Not all container-closures components qualify as medical devices (e.g. sterile vials). <i>Proposed change</i> Delete sentence in lines 358-359.	The comment is acknowledged. The guideline text has been amended accordingly
524	L360	6	In case the CE marked device is in direct contact with the medicinal product it should be assured that the sterility of the device adheres to PhEur/EMA definition. This sentence seems to indicate that NB apply the same definition (i.e. sterility requirements). It is questioned whether the approach to accept the certificate of conformity is in line with the guidance given in line 326.	The comment is acknowledged. The guideline text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
525	L360-361	18	<p>Comment: A NB Certificate of Conformity for a sterile CE-marked device does not demonstrate sterility, with Certificate scope and Annex a key consideration so the statement is not accurate. Conformity assessment is based on the capability of a Manufactures QMS system to control design development and manufacture, which may include control of sterilisation processes.</p> <p>Proposed change (if any): <i>Where a sterile CE-marked device is used, the inclusion of the NB Certificate of Conformity shall be accepted as supportive evidence is sufficient to demonstrate sterility.</i></p>	The comment is acknowledged. The guideline text has been amended.
526	L362	14	<p>Comment: Clarification is needed on what is considered as a suitable specification for a device or device component. How does this expectation differ to that in line 356?</p> <p>A PFS would have a specification for the Materials of Construction and critical dimensions of the primary, drug-contacting container closure components. Secondary packaging including device components such as AI/Pen sub-assemblies or more complex administration devices would not have critical attributes for a specification. The device components are controlled during their manufacture and would be qualified by the Sponsor and when sourced from a contracted third party, controlled on receipt as raw materials.</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change: "Suitable quality control specifications of medical device(s) and/or device components when product-contacting. "	
527	L362	28	Comment: Remove: "shall be covered via GSPR", otherwise a simple device change can trigger a drug variation – very ineffective and not adding value	The comment is acknowledged. No change to the guideline text is proposed.
528	L363-366	28	Comment: Remove: To request information on all device components and specifications is unnecessary. These aspects would have been covered by the process of assessing the conformity with the General Safety and Performance Requirements (Annex 1, 2017/745 MDR) by the manufacturer or the Notified Body. Limit to components and materials in contact with the medicinal product. Otherwise a simple device change can trigger a drug variation – very ineffective and not adding value. For the same reason's photographs should not be included.	The comment is acknowledged. No change to the guideline text is proposed.
529	L363-366	31	Comment: The guideline states that detailed test procedures should be located in the P.7 section. However, test methods for the DDC for release and stability are expected to be located in P.5.2, and other tests relevant to verification of the device design and performance are better located in 3.2.R where other device descriptions and relevant performance information are located. Critical dimensions, for primary packaging components/components with direct drug product	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>contact, representative drawing and photographs have typically been sufficient registration information for the P.7 section.</p> <p>Proposed change: Consider deleting the requirement to provide test methods in P.7</p>	
530	L363-365	14, 31	<p>HIGH PRIORITY Comment: Concern regarding duplication of assessment. The responsibility for device components not in direct contact with the drug product should reside with the NB. Thus, detailed information on these components should not be needed in the MAA. Photographs should also not be required in addition to technical drawings as they add no further value.</p> <p>Indeed, “as well as critical dimensions, technical drawings” – this is significantly more detail than what is currently required or indeed needed or useful, unless the device is a primary container. The guideline states that detailed test procedures should be located in the 3.2.P.7 section. However, test methods for the DDC for release and stability are expected to be located in 3.2.P.5.2, and other tests relevant to verification of the device design and performance are better located in 3.2.R where other device descriptions and relevant performance information are located.</p> <p>Proposed change: Replace lines 363-366 with: “For device components not in direct contact with the drug product only summary information should be</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>included in the MAA, i.e. no requirement to include detailed specification or detailed drawings on these device components.</p> <p>Schematics illustrating assembly and/or use are sufficient and should be provided as needed. Detailed specifications and test proceduresmechanical resistance of the DDC"</p>	
531	L363-365	16	<p>Guideline Section P.7 Container Closure system require the applicant to provide detailed information in the MAA. Since detailed information of the device design can be proprietary information not to be exposed to other companies more tools and guidance are needed.</p> <p>Proposed change (if any): To protect confidential information between collaborating companies an additional submission procedure to transfer this information directly to NB and/or CA (similar to Active Substance Master File procedure, for device, e.g. FDA Device Master File) should be developed and described.</p>	The comment is acknowledged, however, there is no legal provision currently for a device master file in European legislation. No change in the guideline text is proposed.
532	L364	28	<p>Comment: 'Critical dimensions' is too generic.</p> <p>Proposed change (if any): Delete "critical dimensions" because risk management applies – and specification is already stated</p>	The comment is acknowledged; however, "critical dimensions" is the term used in the Notice to Applicants Vol 2B (see comment 520). No change to the guideline text is proposed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
533	L365	14	<p>Comment: Clarification is sought as to what is considered 'functional secondary packaging materials' as autoinjectors or similar are considerably more than 'functional secondary packaging',</p> <p>Proposed change: Definition of functional secondary packaging.</p>	The comment is acknowledged. No change to guideline text is proposed.
534	L367	28	<p>Comment: Reference to current Ph.Eur. should be sufficient rather than providing evidence of compliance.</p>	The comment is acknowledged. No change to guideline text is proposed.
535	L367-368	14	<p>Comment: Evidence of relevant monograph compliance should be ensured through device specifications when forming part of the potentially product-contacting primary packaging. Compliance declaration from suppliers are currently considered GMP information. By analogy, DP excipient compliance to monograph are not supported by supplier declarations in the submission. If supplier declarations are required, supplier changes during the lifecycle would require the submission of a variation. Suppliers may change but compliance to monograph remains unchanged. This bullet apparently repeats how line 356 could be interpreted. Added text is suggested to cover when a material is not compendial.</p> <p>Proposed changes:</p> <ol style="list-style-type: none"> Delete reference to specification in line 356. "Evidence of compliance for potentially product-contacting materials of construction with the relevant 	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Ph. Eur. Monographs, if applicable, and/or food contact Directives, as appropriate (such as declarations of compliance from suppliers). Any drug-contacting material of construction that is not meeting compendial standards should include a specification."	
536	L367-368	9	<p><u>Original Text</u> <i>Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, as appropriate (such as declarations of compliance from suppliers).</i></p> <p><u>Proposed Changed Text</u> <i>Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, as far as packaging materials for non-solid active substances and non-solid medicinal products intended for oral and topical (except ophthalmic) administration are concerned (refer to EMEA guideline on plastic immediate packaging materials), as appropriate (such as declarations of compliance from suppliers).</i></p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
537	L367-368	11	<p>Comment: Food contact Directives is not considered suitable for device components. Evidence of compliance with relevant monograph or iso standards should be considered as more relevant</p> <p>Proposed changes: Evidence of compliance with the relevant Ph. Eur. Monographs and in second intention with harmonized standards as appropriate (such as declarations of compliance from suppliers).</p>	The comment is acknowledged; the wording has been revised to state 'primary packaging materials of construction should be described and comply with the relevant Ph. Eur. monographs, if applicable, and food contact directives, as appropriate (e.g. evidenced by declarations of compliance from suppliers).
<u>5. INTEGRAL DDCs – 5.2. MODULE 3.2.P.8 – STABILITY (L369-379)</u>				
538	L369	5	See 211. Also need to clarify what is required from a device point of view with respect to stability and therefore the NB review. Especially as NB may be reviewing before pivotal stability data is ready.	The comment is acknowledged. The guideline text has been amended accordingly
539	L369	10	<p>Comment: Container closure integrity testing should also be part of the stability testing.</p> <p>Proposed change: Container closure integrity testing, in order to ensure maintained freedom from defects (like cracking or leaking) over the expected shelf life.</p>	The comment is acknowledged. The guideline text has been amended accordingly

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
540	L369-379	27	EFA would propose that stability studies should also look into the loss of functionality/stability when there has been a bad use or bad process of maintaining and/or cleaning of the DDC.	The comment is acknowledged. No change to guideline text is proposed.
541	L371-373	14	<p><u>HIGH PRIORITY</u></p> <p><u>Comment:</u></p> <p>Section P.8 typically only includes testing that is formally part of the drug stability program, which is intentionally limited, and not including any shelf life testing that is formally part of Device Verification Testing (typically located in 3.2.R) and only conducted one time.</p> <p>For a DDC P.8 section, the information should be focused on the stability-indicating device functionality CQAs through shelf-life per ICH conditions. Drug stability in the primary container closure system would be cross-referred to the appropriate CTD P.8 section. Device stability could be located in 3.2.R along with specific ISO etc testing that differ from ICH described drug stability. How shelf-life of the DDC is determined should be outlined?</p> <p>Functionality tests in the formal stability program should be justified by the Sponsor as CQAs rather than listing in guidance. Examples carry a risk of being interpreted as required CQAs. Furthermore, some examples provided can be considered as alternatives, e.g. 'syringeability' could be part of the extractable volume test or dose delivery.</p> <p>Moreover, it is requested to avoid 'new' words such as 'syringeability' which may not be understood and also implies</p>	<p>The comment is acknowledged.</p> <p>The wording has been revised, with reference to 3.2.P.2.4.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>tests that the EU has never before required as a CQA at release or stability.</p> <p>The deletion of example functionality tests makes the following sentence redundant and should be deleted. Furthermore, integral ingestible devices are not DDCs (same comment as for line 80)</p> <p>Proposed change:</p> <p>"Functionality tests determined as stability-indicating CQAs (e.g. does delivery per actuation, syringeability, communication with software, etc.). In the case of complex DDCs medicinal product are required."</p>	
542	L374-375	14	<p>Comment:</p> <p>It is not clear how 'in use' testing is different to the 'functionality tests'. The functionality testing, through shelf-life, should be performed under 'in use' conditions as stated in the SmPC. Any 'in use' stability that is not part of the formal stability program and performed once to qualify the DDC would be in 3.2.P.2.6 or 3.2.R.</p> <p>Proposed change:</p> <p>"Functionality tests In-use stability testing performed under in-use the conditions of use as stated in the SmPC, unless otherwise justified."</p>	<p>The comment is acknowledged.</p> <p>It is not agreed. In-use stability testing is the commonly used term for medicinal products (refer to the Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)). The wording has been revised to ensure functionality tests are considered.</p>
543	L376-377	14	<p>HIGH PRIORITY</p> <p>Comment:</p> <p>Particular stability tests are being prescribed that should be determined to be CQAs and stability-indicating by the</p>	<p>The comment is acknowledged.</p> <p>Examples are provided to be informative and are clearly indicated as being not exhaustive. The wording has been revised to refer to CQAs,</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>sponsor. The text seems to acknowledge certain tests may be justified not to be included but this is not clear and “as appropriate” may not be understood.</p> <p>Furthermore, the intention of the term “content/potency” is not clear. Flexibility should be allowed to perform such testing on the primary container closure if it can be justified that final assembly of the DDC does not impact these attributes.</p> <p>The schedule of drug attribute testing using a DDC, that is additional to the formal drug stability program, should be justified on a risk basis and may be a reduced program compared to the drug stability schedule.</p> <p>It is a concern that the text could be understood as performing sterility testing at every time point through shelf-life whereas the current expectation is at shelf-life.</p> <p>Furthermore, consideration should be allowed for appropriate scientifically justified alternatives for sterility, such as container closure integrity testing.</p> <p>Note that DDCs such as autoinjectors and pens cannot be sterility tested as the plastic shells prevent sample decontamination prior to introduction into the isolator. Hence, CCI testing is carried out in lieu.</p> <p><u>Proposed change:</u></p> <p>“On a risk-based, justified program, identified drug stability-indicating CQAs Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate. Appropriate, scientifically</p>	<p>however some examples are retained for guidance purposes.</p> <p>The wording has been revised in relation to the possibility to perform alternative testing.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			justified alternatives for sterility, such as container closure integrity testing may be used.”	
544	L376-377	20	<p><u>Comment:</u></p> <p>The EMA has adopted ICH guideline Q1E on the evaluation of stability data for medicinal products, which allows, under certain circumstances, for extrapolation to extend the retest period or shelf life beyond the period covered by long-term data, particularly if no significant change is observed at the accelerated condition. However, the current draft guideline requires “Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate”, which implies that extrapolation of stability data will not be acceptable for a DDC.</p> <p><u>Proposed change:</u></p> <p>State definitively whether or not extrapolation of stability data may be acceptable when establishing the shelf life or retest date for a DDC, depending upon the specific characteristics of the product.</p>	<p>The comment is acknowledged.</p> <p>DDCs are not excluded from ICH stability guidance and it is not the intention of this guideline to imply that. The wording has been revised to clarify this.</p>
545	L378	14	<p><u>HIGH PRIORITY</u></p> <p><u>Comment:</u></p> <p>Transportation of the DDC is qualified in 3.2.P.3.5 and typically includes simulated transport. Section 3.2.R could also include simulated transport per ASTM conditions. When transport has no impact, no further stability evaluation should be necessary. It is not considered required or of value</p>	<p>The comment is acknowledged.</p> <p>The text has been moved to clarify the intent.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>to perform stability over shelf-life once transportation has been validated.</p> <p>Proposed change:</p> <p>Move lines 378 – 379 to section 3.2.P.3.5:</p> <p>it is important to clarify that simulated transport data are not linked to or expected as part of the stability data collected through shelf-life.</p>	
546	L378-379	9	<p>Original Text:</p> <p><i>Simulated transport studies that encompass chemical (e.g. degradation) and physical (e.g. vibration) stability, where relevant.</i></p> <p>Comment:</p> <p>The original text is confusing, as degradation is what may be measured, and vibration is a process – the revised wording provides examples of things which cover chemical and physical aspects of transportation and also mentions the potential for actual transportation.</p> <p>Proposed change:</p> <p><u>Actual transportation or simulated transport studies that encompass chemical (e.g. different temperatures) and physical (e.g. vibration) stability aspects to demonstrate stability during transportation, where relevant.</u></p>	<p>The comment is acknowledged (see also comment 545).</p> <p>The wording has been moved and revised.</p>
<u>5. INTEGRAL DDCs – 5.3. MODULE 3.2.A.2 – ADVENTITIOUS SAFETY EVALUATION (L380-400)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
547	L380	24	<p>5.3. Module 3.2.A.2, Adventitious Safety Evaluation</p> <p><u>Comment</u></p> <p>The word "Agents" is missing.</p> <p><u>Proposed change:</u></p> <p>5.3. Module 3.2.A.2, Adventitious Agents Safety Evaluation</p>	<p>The comment is acknowledged.</p> <p>The wording has been revised.</p>
548	L381-384	14, 31	<p><u>Comment:</u></p> <p>Animal derived materials [e.g., highly process tallow derivatives (e.g., stearates)] are commonly use as mould release agents for certain component parts of devices. Their sources or identities may not always be known for integral or kitted devices (with CE marks) although relevant certificates for ISO and Ph. Eur. may sometimes be obtained from the suppliers. The patient risk related to internal non-contacting device component is negligible and patient contacting surfaces may constitute no greater risk than many consumer products.</p> <p><u>Proposed change:</u></p> <p>Consider limiting this requirement to drug contacting surfaces: "All materials of human or animal origin used in the manufacturing process of the final assembly of the DDC, or such materials coming into contact with the device drug-contacting surfaces during its manufacturing process, should be identified."</p>	<p>The comment is acknowledged.</p> <p>The wording has been revised in line with this and comment 549.</p>
549	L385	5	<p><u>Comment:</u></p>	<p>The comment is acknowledged.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			If the Competent Authority are reviewing this, then GSPR 13.2 is not relevant?	The wording has been revised in line with this and comment 548.
550	L386-390	14	<p>Comment:</p> <p>Edit for clarity</p> <p>Proposed change:</p> <p>Where appropriate, a TSE statement confirming compliance of the component(s) of the DDC with EMEA/410/01 rev.3, to the European Standard "Medical devices utilising animal tissues and their derivatives – part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents (EN ISO 22442-3:2007)" and Ph. Eur. 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" should be provided in this section.</p>	<p>The comment is acknowledged.</p> <p>The text has been revised.</p>
551	L392-395	14	<p>Comment:</p> <p>Edit for clarity</p> <p>Proposed change:</p> <p>Where applicable, an assessment of the risk to the DDC with respect to potential viral contamination should be provided in this section.</p> <p>The viral risk assessment should be made in accordance with the European Standard "Medical devices utilizing animal tissues and their derivatives – part 3 1 Application of risk management (EN ISO 22442-1:2015)" and Ph. Eur. 5.1.7 Viral safety.</p>	<p>The comment is acknowledged.</p> <p>The text has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>5. INTEGRAL DDCs – 5.4. MODULE 3.2.R. – REGIONAL INFORMATION, MEDICAL DEVICE (L401-462)</u>				
552	L401	5	<p><u>Comment:</u></p> <p>The description on the content of this section is confusing and not fully consistent with table 1 of EMA Q&A dated Feb. 2019.</p> <p>Does this part include:</p> <ul style="list-style-type: none"> - the applicant’s demonstration of compliance of the device with MDR annex 1 GSPR AND the results of the assessment of the compliance (DoC/NB certificate/NBOp)? <li style="text-align: center;">or - the results of the assessment of the compliance only? <p><u>Proposed change:</u></p> <p>Provide clarifications on the documentation expected in part 3.2.R</p>	<p>The comment is acknowledged.</p> <p>The text has been reviewed and revised for clarity.</p>
553	L401	5	<p><u>Comment:</u></p> <p>“Section 3.2.R should include information related to demonstration of compliance of the device with MDR annex 1 GSPR”</p> <ul style="list-style-type: none"> ○ How does the applicant have to present this demonstration? ○ Does EMA consider that this demonstration should be presented like a technical file as set out in annex II of the MDR (like stand alone MD to certify)? 	<p>The comment is acknowledged.</p> <p>The wording has been reviewed for clarity.</p> <p>3.2.R refers to what will be provided to CA for review, not NB. The format of what is submitted to NB is out of scope of this guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> ○ Is a specific guidance foreseen? Or does EMA consider that each NB can have its own requirements? ○ Does section 3.2.R correspond to the documentation that will be reviewed by the NB in case of a NBOp? <p>Proposed change:</p> <p>Provide clarifications on the presentation of the demonstration of compliance of the device with MDR annex 1 GSPR</p>	
554	L401-403	14	<p>Comment:</p> <p>3.2.R states; 'An index should be provided, which should cross refer to studies or information provided in 3.2.P and Module 5 sections as appropriate'. However, Line 408-411 states that if a device is Class IIa/b then 3.2.R should contain NBOp.</p> <p>Subsequent text below (lines 404 to 459) seems to indicate that only a relatively small number of documents would reside in 3.2.R for the device, so the provision of an index should be optional based on product/dossier need.</p> <p>Please clarify whether information should be included as notes in Module I or both. Currently this is managed by notes to reviewer in Module I. Please state whether this is to be duplicated in 3.2.R.</p> <p>Proposed change:</p> <p>Suggest Lines 402-403 are removed for clarity.</p>	<p>The comment is acknowledged.</p> <p>The lines have been deleted.</p>
555	L401-419	17	<p>Comment:</p>	<p>The comment is acknowledged.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Regeneron appreciates the Agency's efforts to provide guidance on the contents of Section 3.2.R in the context of compliance with MDR Annex 1. To further the robustness of this guideline, we ask that the Agency explicitly differentiate Sections 3.2.P and 3.2.R by providing specific examples of what kinds of information should be included in Section 3.2.R and not in Section 3.2.P.</p> <p><u>Proposed change:</u></p> <p>None</p>	<p>It is not agreed. Covering many examples would cause the guideline to be too lengthy. Since there is such a wide variety of devices, it is considered appropriate to keep the guideline as simple as possible for clarity.</p>
556	L404-405	30	<p><u>Comment:</u></p> <p>Please note, for Integral DDC's, the term "device(s)" is already mentioned in lines 404-405, through which we understand that EU declaration of conformity/ Notified body Certificate of Conformity is required for <u>all</u> the components (if any) of Integral DDC's. <u>Please confirm.</u></p>	<p>The comment is acknowledged.</p> <p>The text has been reviewed and revised for clarity.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
557	L404-417	14	<p>Comment:</p> <p>Applicant should include information in Section 3.2.R related to demonstration of compliance of the device(s) with Annex 1 of the MDR.</p> <p>Is there any provision for providing statement that the device is undergoing NBOP or must this be done ahead of submitting the MAA? Q&A from Feb'19 suggests the NBOP could be provided after MAA submission itself.</p> <p>Proposed change:</p> <p>Clarify if NBOP can be concurrent with MAA review (at least provided later) and what statement should be provided in these instances within 3.2.R.</p>	<p>The comment is acknowledged.</p> <p>Procedural timing aspects are out of scope of the guideline. Reference is made to the EMA Q&A for clarification. No change to the text is made.</p>
558	L406	14	<p>Comment:</p> <p>Many CAPs (conformity assessment procedures) result in multiple certificates, one for the QMS and another for the device. Please could the agency clarify which certificate should be presented?</p>	<p>The comment is acknowledged.</p> <p>The certificate to confirm the conformance of the device with the relevant GSPRs should be presented. Since this is stated in the preceding paragraph, no change to the text is made.</p>
559	L406-407	28	<p>Comment:</p> <p>Delete "Where available, an EU Declaration of Conformity issued by the device manufacturer, or a Certificate of Conformity issued by a NB that allows a CE mark to be displayed on the device" as this is not relevant for an integral DDC.</p>	<p>The comment is acknowledged.</p> <p>If the intended use of the device in the integral product was the same as described on the Certificate of Conformity allowing a CE mark to be displayed on the device, this would be sufficient to demonstrate compliance with the relevant GSPRs. The text is in line with Article 117 of the MDR and is retained.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
560	L406-407 and L553-555	14	<p>Comment:</p> <p>Under 406-407 it says that a Declaration of Conformity (for Class I) or a Certificate of Conformity (for classes above Class I) should be submitted to demonstrate compliance in case of CE mark, whereas under 553-555 it says that for risk classes above Class I also a Certificate of Conformity should be provided. This implies there that for classes above I, the Certificate of Conformity is not sufficient but a Declaration of Conformity is also needed.</p> <p>Proposed change:</p> <p>Harmonise wording and requirements to ensure consistency.</p>	<p>The comment is acknowledged.</p> <p>Text has been revised for accuracy and consistency.</p>
561	L408-410	14	<p>Comment:</p> <p>If Certificate of Conformity or Declaration of Conformity is not available, then the following can be provided "(a) If the device is a class I device (excluding Im, Is, Irsi): the applicant's confirmation that the device part meets the relevant GSPRs..."</p> <p>Proposed change:</p> <p>Clarify what form the confirmation would take, i.e. what is meant by "the applicant's confirmation". For example, line 417 states that for ATMPs, the applicant can provide a checklist. Should this be a formal Applicant Declaration of Conformity, or simply a sentence written into the text of 3.2.R?</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the text of the final guideline and updated Q&A (June 2021) on the MDR implementation.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
562	L409 and L411	14	<p>Comment:</p> <p>A reference to the medical device risk classification rules, MDR Annex VIII, would be helpful.</p> <p>Proposed change:</p> <p>Add a reference to the medical device risk classification rules, MDR Annex VIII</p>	<p>The comment is acknowledged.</p> <p>MDR Classification rules are considered outside the scope of this guideline. Reference is made to the updated EMA Q&A (June 2021) on the MDR implementation.</p>
563	L409	14	<p>Comment:</p> <p>Over abbreviated: (excluding Im, Is, Irsi)</p> <p>Proposed change (if any):</p> <p>These abbreviations should be spelt out in full.</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the updated EMA Q&A (June 2021) on the MDR implementation.</p>
564	L409	5	<p>Comment:</p> <p>Class Im, Is, Irsi are not in the list of abbreviations (Ir instead of Irsi?)</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the updated EMA Q&A (June 2021) on the MDR implementation.</p>
565	L409	28	<p>Comment:</p> <p>In line 154 guideline refers to details in 5.4 Module 3.2.R; however, those guidelines do not guide sufficiently for integral DDC because these medical device components are not classified: I, Im, Is, Irsi; IIa, IIb or III on its own right. Reference to "if used separately" should be further elaborated. Classification rules applies to (CE-Marked) Medical Devices only.</p> <p>Guideline should support manufacturers in their decision:</p> <ul style="list-style-type: none"> - NBOp is needed and 	<p>The comment is acknowledged.</p> <p>"If used separately" is wording taken directly from the MDR and refers to the classification of the device were it to be used separately as a medical device in its own right.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>- Applicants own confirmation is adequate</p> <p>Current draft indicates that majority of Integral DDC's would require a NBOP; however, allows for Integral DDC's where device components has a low risk to self-declare.</p> <p><u>Proposed change:</u></p> <p>see row below</p>	
566	L409	28	<p><u>Comment:</u></p> <p>See comment row above</p> <p><u>Proposed change:</u></p> <p>Add:</p> <p>For Integral DDC's the device part is not classified on its own right. Therefore, for an integral DDC, manufacturer must justify its assessment of "associated Medical Device Class" and involve NB's accordingly.</p> <ul style="list-style-type: none"> • "Associated Class I" compares to Class I as described in MDR Annex VIII. Such medical device components do not require NB involvement. Integrated DDC's in "Associated Class I" are those low risk device components that are not "Other Classes Associated" • "Other Classes Associated" compares to Classes Im, Is, Irsi; IIa, IIb or III as described in MDR Annex VIII. Such medical devices components require NB involvement. <p>Medical Device components in these classes includes the following:</p>	<p>The comment is acknowledged.</p> <p>MDR Classification rules and associated text are considered outside the scope of this guideline. Refer to the EMA Q&A.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Implanted, Active, Invasive (except reusable surgical instruments), Components that incorporate or consists of nanomaterials.</p> <p>The following Non-invasive medical device components:</p> <ul style="list-style-type: none"> - Those that, may be connected to active devices, intended for channeling or storing blood, body liquids, cells or tissues, liquids or gasses for the purpose of eventual infusion, administration or introduction into the body - Those that are intended for channeling or storing blood or body liquids or storing organs, parts of organs or body cells and tissues including blood bags - Those intended for modifying the biological or chemical composition of human tissue or cells, blood, other body liquids or other liquids intended for implantation or administration into the body - Those that are in contact with injured skin or mucous membrane if they are used principally for injuries to skin which have breached the dermis or mucous membrane and can only heal by secondary intent <p>Those that are in contact with injured skin or mucous membrane if they are principally intended to manage the micro-environment of injured skin or mucous membrane.</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
567	L409-410	19	<p><u>Comment:</u></p> <p>The mechanism for 'applicant's confirmation' is not defined.</p> <p><u>Proposed change:</u></p> <p>Clarify expectations for the confirmation. Should this be a formal Applicant Declaration of Conformity, or simply a sentence written into the text of 3.2.R?</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 561.</p>
568	L411	5	<p><u>Comment:</u></p> <p>It is not clearly indicated if the NBOp shall be positive or whether a negative/ in-conclusive result is possible. or not favourable.</p> <p>If the NB concludes that the device is not fully compliant with the GSPR or that the data provided are not sufficient to make a a conclusion, is the applicant then allowed to submit the MAA to the NCA/EMA? Is a negative conclusion in a NBOp or inconclusive NBOp acceptable in a submitted MAA?</p> <p>If questions remain, will these then be assessed by the NCA/EMA?</p> <p><u>Proposed change:</u></p> <p>Provide clarity on the assessment results expected in the NBO to be included in a submitted MAA dossier</p>	<p>The comment is acknowledged.</p> <p>The overall conclusion of the NB opinion is expected to demonstrate full compliance of the device constituent(s) with the relevant GSPRs in MDR Annex 1. If not, this would result in a major objection and would impact on the approvability of the MAA.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
569	L411	5	<p><u>Comment:</u></p> <p>It is stated that for Class Im and Is a NBOp on the conformity of the device with relevant GSPRs is needed. Currently, NB's do not assess all essential requirements / GSPR's from a Class Is or Class Im device. The focus of the review for Class Im and Is is limited to those essential requirements relating to respectively the measuring function and the sterility (and maintenance of the sterility). Can EMA confirm that the current approach is acceptable since the other essential requirements and GSPRs from a Class I are out of scope of the assessment of a NB (see rule 409/410)?</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 565. No change to the text has been made.</p>
570	L411	14, 31	<p><u>Comment:</u></p> <p>Please clarify that this sentence is referring only to single integral DDC products and not medical devices under MDR 2017/745.</p>	<p>The comment is acknowledged.</p> <p>The highlighted text relates to single integral products only as per the headings in the guideline. The wording has been revised to clarify this.</p>
571	L411 and L554	14	<p><u>Comment:</u></p> <p>For device classifications, "Irsi" is listed, but that is not how the device world has typically listed this classification (Class I reusable).</p> <p><u>Proposed change:</u></p> <p>Typically, it is referred to as "Ir", not "Irsi".</p>	<p>The comment is acknowledged.</p> <p>The abbreviations have been clarified.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
572	L411-412	14	<p>Comment:</p> <p>Under MDD, the conformity of a class Im/Is device may be assessed by the manufacturer, with a Notified Body involved for assessment of the measuring/sterility aspects, respectively. Integrated devices were able to be assessed by the Applicant.</p> <p>It appears EMA are interpreting that under MDR, an integrated Class Im/Is device would need a 'full' Notified Body Opinion rather than simply review of the measuring/sterility aspects. This increases the requirements for certain Class I devices. Please could the agency clarify what level of Notified Body review is required for integral "class Im/Is" devices and confirm whether this is supported by Notified Bodies/NBOG/TEAM-NB?</p>	<p>The comment is acknowledged.</p> <p>Refer to comments 561, 565 and 569.</p>
573	411-412	19	<p>Comment:</p> <p>Under MDD, the conformity of a class Im/Is device may be assessed by the manufacturer, with a Notified Body involved for assessment of the measuring/sterility aspects, respectively. Integrated devices were able to be assessed by the Applicant.</p> <p>It appears EMA are interpreting that under MDR, an integrated Class Im/Is device would need a 'full' Notified Body Opinion rather than simply review of the measuring/sterility aspects. This increases the requirements for certain Class I devices. Is this supported by Notified Bodies/NBOG/TEAM-NB?</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 561, 565 and 569.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
574	L412	6	<p>Comment:</p> <p>How can 'appropriately designated' be identified by applicants or assessors?</p>	<p>The comment is acknowledged.</p> <p>The designation of the NB may be checked on the NANDO website.</p>
575	L413-417	18	<p>Comment:</p> <p>ATMPs should be excluded from this guideline as they are stated as being out of scope of this document within section 2. Additionally, the approach of considering a device as a container closure system is not in-line with the approach taken for other (non ATMP) medicinal products</p> <p>Proposed change:</p> <p>Remove paragraph</p> <p>3. For medical devices that are used as container closure system for ATMPs, the applicant should provide evidence that the relevant GSPRs are met, as follows:</p> <p>(a) EU Declaration of Conformity issued by the device manufacturer, or</p> <p>(b) Certificate of Conformity issued by a NB, or</p> <p>(c) Confirmed by the applicant (e.g. by providing summary information in form of checklist).</p>	<p>The comment is acknowledged.</p> <p>Article 117 of the MDR does not apply to ATMPs. However, the marketing authorisation application for an ATMP should contain information about the device constituent information as outlined in the guideline (see under Scope).</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
576	L413-417	24	<p>Comment:</p> <p>It seems that for medical devices that <u>are used as container closure system</u> for ATMPs, the applicant may provide evidence that the relevant GSPRs are met by submitting</p> <ul style="list-style-type: none"> • an EU Declaration of Conformity <i>issued by the device manufacturer, or</i> • by submitting a <i>Certificate of Conformity issued by a NB, or</i> • by submitting a <i>confirmation which was issued by the applicant itself.</i> <p>Proposed change</p> <p>It should be clarified, that the applicant’s confirmation would only be appropriate for medical devices that - if used separately - do not require the involvement of a Notified Body. This is in compliance with the requirements for “non-ATMP single-integral DDCs”.</p>	<p>The comment is acknowledged.</p> <p>The text has been revised.</p>
577	L415-417	10	<p>Comment:</p> <p>It seems that for medical devices that are used as container closure system for ATMPs, the applicant may provide evidence that the relevant GSPRs are met by submitting</p> <ul style="list-style-type: none"> • an EU Declaration of Conformity <i>issued by the device manufacturer, or</i> • by submitting a <i>Certificate of Conformity issued by a NB, or</i> 	<p>The comment is acknowledged.</p> <p>Refer to comment 576.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> by submitting a <i>confirmation which was issued by the applicant itself</i>. <p>It should be clarified, that the applicant's confirmation would only be appropriate for medical devices that - if used separately - do not require the involvement of a Notified Body. This is in compliance with the requirements for "non-ATMP single-integral DDCs".</p>	
578	L417	10, 24	<p>Comment:</p> <p>It should be made clear that the "checklist" should be in compliance with the Annex I of the MDR, as applicable.</p> <p><i>("(c) Confirmed by the applicant (e.g. by providing summary information in form of checklist")</i>.</p>	<p>The comment is acknowledged.</p> <p>Reference to MDR Annex I (the applicable GSPRs) is already made in this section and so is not repeated here.</p>
579	L417	10, 24	<p>Comment:</p> <p>It should be made clear that "summary information" does not require the submission of raw data/reports.</p> <p><i>("(c) Confirmed by the applicant (e.g. by providing summary information in form of checklist")</i>.</p>	<p>The comment is acknowledged.</p> <p>The term "summary information" is considered to indicate that raw data/reports are not expected.</p>
580	L417 and L149-150	10, 24	<p>Comment:</p> <p>For medical devices that are used as container closure system for ATMPs it seems appropriate to submit a confirmation by the applicant that the GSPRs are met; e.g. by providing a summary of information in form of a checklist (see line 417).</p> <p>Proposed change:</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 579.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			It should be made clear that the applicants' confirmation in accordance with Article 117 of the MDR (see line 149 - 150) may also be provided by submitting a summary information in form of a checklist. Within this context, "summary information" should be clarified (see comment above)	
581	L418-419	21	<p><u>Comment:</u></p> <p>The person who signs the document must be able, based on the experience or background, to be able to give credibility to what is described in the document. Proposed to add the responsible person for the compliance of the medical devices, art.15 of Eur Reg. 2017/745 after the qualified person for medicinal product for human use.</p>	<p>The comment is acknowledged.</p> <p>A device in an integral product does not need to comply with the whole MDR (just the relevant GSPRs in Annex I). No change to the text is proposed.</p>
582	L421-438	14, 19	<p><u>Comment:</u></p> <p>Repetitive content, already covered several times within the rest of the guideline.</p> <p><u>Proposed change (if any):</u></p> <p>Remove all 3 paragraphs.</p>	<p>The comment is acknowledged.</p> <p>Revision has been performed to reduce repetition where possible.</p>
583	L431	22	<p><u>Comment:</u></p> <p>It would be helpful if this guidance provided slightly more detail regarding notified body opinion (NBO) requirements. For instance, in the case of multi-component drug and device combinations, is it sufficient to combine separate NBOs from the device constituent manufacturers, or must the applicant submit an NBO for the overall combination in the drug MAA? As an example, a prefilled autoinjector may be made of purchased syringe barrels and autoinjector parts. Would an NBO be required for the syringe and autoinjector assembled</p>	<p>The comment is acknowledged.</p> <p>The format of the NBOp is the responsibility of the NB. Reference is made for example to the TeamNB position paper "Proposal for a NBOp template".</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>as a single unit, or would separate assessments be required for each component (i.e. one opinion for the syringe, one opinion for the autoinjector)?</p> <p>Similarly, can a manufacturer obtain a single NBO for a platform device that is intended to be used in Integral DDCs with multiple drug products and indications, provided that the data provided to support the NBO covers the range of characteristics of multiple drug products/indications (e.g., testing with a range of viscosities, usability testing covering different patient populations concerned)?</p>	
584	L437-438	6	<p><u>Comment:</u></p> <p>How can 'appropriately accredited' be ensured by applicants or assessors?</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 574.</p>
585	L437-438	14	<p><u>Comment:</u></p> <p>Additional clarification required about what exactly constitutes an "appropriately accredited" NB?</p> <p>Which device types align with these devices since there are no specifically designated medical device codes for DDCs, and NB's by definition cannot therefore be accredited.</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 574.</p>
586	L437-438	18	<p><u>Comment:</u></p> <p>Regarding the sentence that states "<i>It should be ensured that the NB is appropriately accredited for the issuance of such an opinion.</i>"</p>	<p>The comment is acknowledged</p> <p>Refer to comment 574. Text has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>It is not clear who is responsible for ensuring the validity of the NB accreditation or what form this "accreditation" shall take.</p> <p>As the NB opinion is contained with the MDR it is assumed that the NB shall have to be designated to the requirements of MDR 2017/745, in order to be able to provide an opinion, however, please note that the scope of designation shall be as per NBOG guidance (F 2017-3) and for technology e.g. "MDA 0306 – Active non-implantable devices for extra-corporal circulation, administration or removal of substance and haemapheresis" rather than Article 117.</p> <p><u>Proposed change:</u></p> <p>replace the word "accredited" with "designated"</p> <p><i>The applicant it should be ensured that the NB is appropriately accredited designated for the issuance of such an opinion</i></p>	
587	L439	14	<p><u>Comment:</u></p> <p>Is it intended to issue a guideline related to the NB opinion process?</p>	<p>The comment is acknowledged.</p> <p>The NB opinion process is out of scope of this guideline.</p>
588	L439	5	<p><u>Comment:</u></p> <p>«the processes by which a NB derives their opinion are not within the scope of this guideline»</p> <p>Is a dedicated guidance foreseen?</p>	<p>The comment is acknowledged</p> <p>Refer to comment 587.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
589	L439-444 and L795-800	14	<p>Comment:</p> <p>In order to avoid duplication of assessment EMA suggests to provide a technical summary report established by the NB, without any further detail of the content, what EMA expects.</p> <p>It is strongly recommended to provide more detailed information here or in Annex 1 of this guidance, which information should be included in the NB assessment report for EMA to feel comfortable to rely on the NB assessment, in particular the assessment of the safety and performance of the device which could impact safety, efficacy and performance of the medicine.</p>	<p>The comment is acknowledged.</p> <p>The guideline has been written to avoid duplication where possible.</p>
590	L440	14	<p>Comment:</p> <p>Recommend to specify as "integral DDC"</p> <p>Proposed change (if any):</p> <p>"...review of the integral DDC..."</p>	<p>The comment is acknowledged.</p> <p>Text has been revised.</p>
591	L441-442	8	<p>Comment:</p> <p>This sentence can be understood that also devices still need a Notified Body opinion, when those devices have already fulfilled the MDR Requirements and which bear a legally affixed CE mark. We ask to clarify if that should be the meaning or if the Notified Body opinion is only needed in cases where a device was not subjected to a separate conformity assessment procedure in accordance with the Medical Device Regulation (Article 52 of Regulation (EU) 2017/745), what may be the case if the manufacturer has no intention to place the Device separately on the market.</p>	<p>The comment is acknowledged.</p> <p>Section 5.4 of the guideline has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
592	L442	10	<p><u>Comment:</u></p> <p>Is it expected that we submit a technical report issued by the NB or written by the company? The annexes are brief. Some additional guidance would be appreciated. A flow diagram for clarity would be beneficial in describing the process.</p>	<p>The comment is acknowledged.</p> <p>The guideline provides sufficient guidance in this regard.</p>
593	L442-444	18	<p><u>Comment:</u></p> <p>Each NB has their own report format and templates and often use a NB specific electronic system for final format and approval, so while the proposition to harmonise format is a nice proposal in practise the danger is that this guideline and the NBOp format becomes a mandated expectation.</p> <p><u>Proposed change:</u></p> <p>Remove Annex I and II from the guideline document</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 583.</p>
594	L443-444	20	<p><u>Comment:</u></p> <p>We appreciate and support the EMA's efforts to promote harmonisation of the format of Notified Body Opinions by publishing a proposed template, and we encourage the Agency and the European Commission to take further steps to ensure the use of an agreed template by Notified Bodies designated under Regulation (EU) 2017/745.</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 583.</p>
595	L444	11	<p><u>Proposed change:</u></p> <p>Regarding device specific data to be included in this NBOp, It is acknowledged that the Drug Product Manufacturer may be able to leverage data of the Device Manufacturer when available.</p>	<p>The comment is acknowledged.</p> <p>It is not considered necessary to highlight this point here.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
596	L445	5	<p>Comment:</p> <p>Usability (human factor) studies</p> <p>Is such cases (as described in the subsequent paragraph) does the summary of these usability studies provided in part 3.2.R :</p> <ul style="list-style-type: none"> - Are considered to be part of the applicant’s demonstration of compliance of the device with MDR annex 1 GSPR - (thus) Also have to be reviewed by a NB through a NBOp? Or are they only assessed by the EMA/NCA (section 5)? <p>Proposed change (if any):</p> <p>In relation with comments above, provide clarity on documentation submitted to a NB for the purpose of a NBOp (in a separated guidance or not) and scope of the NB assessment or clarity on the scope of the guidance and its limitations</p> <p>Provide clarity on boundary between EMA/NCA and NB scope of assessment.</p>	<p>The comment is acknowledged</p> <p>The assessment of NB and CA will be case specific, and thus it is not considered appropriate to specify the boundaries between NB and CA assessment.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the recommendations of the EMA Regulatory Science Strategy to 2025.</p>
597	L445	14	<p>Comment:</p> <p>Aligned wording with comment above to line 291</p> <p>Proposed change:</p> <p>Usability tests (including human factors) studies studies)</p>	<p>The comment is acknowledged.</p> <p>Text has been revised.</p>
598	L445	14	<p>Comment:</p>	<p>The comment is acknowledged.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			It is our understanding that some notified bodies will be requesting to review human factor/ usability studies. There is therefore a concern around duplication of review between the NCAs and Notified Bodies.	The scope of NB assessment is outside of the scope of this guideline.
599	L445-459	28	<p><u>Comment:</u></p> <p>The content as such is meaningful with regards to a submission but goes beyond the description in the MDR. In this way even minor changes could lead to variations limiting the opportunity for continuous improvement for the benefit of patients. If the inclusion will trigger a drug variation in case of updates, this is effective and value adding, and the text needs to be changed.</p> <p><u>Proposed change:</u></p> <p>Add sentence to line 450: A usability file related to the device constituent part should be maintained</p>	<p>The comment is acknowledged.</p> <p>Guidance regarding lifecycle management is included in the guideline.</p>
600	L445-462	14	<p><u>Comment:</u></p> <p>There is a great overlap of requiring information in the MAA that is already part of Annex I and would therefore already be part of the opinion of the NB.</p> <p>Redundant assessments between CA and NB should be avoided. It should be stated more clearly in the guidance that this information is only to be provided if no NB opinion is provided in the MAA (devices constituent part that would be classified as class I if separately used).</p>	<p>The comment is acknowledged.</p> <p>Reference is made to the core precept of this guideline.</p> <p>The objective of the guideline is to minimise duplication of review by specifying what data is expected in the dossier for marketing authorisation application. But guidance on the content of an application submitted to a Notified Body, or the scope of the review by a Notified Body, is outside EMA remit.</p> <p>The development of an integrated evaluation pathway for DDCs is one of the</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
				recommendations of the EMA Regulatory Science Strategy to 2025.
601	L446-450 (also applies to L565-567)	14	<p>Comment:</p> <p>The description of when usability assessments should be done (line 446) should be expanded to include a broader consideration of the intended user population (who the product is used by rather than just the proposed patient population the device will be used on) and other aspects of intended use. The patient population is not the subject of a Human Factors study. These studies determine that a user can use the device as intended. We believe the author means user population.</p> <p>Additionally, prefilled syringe use (line 448) may not always need to be assessed for commonly used and well-known use scenarios, such as use by an HCP in an outpatient clinical setting. Replacing the example of an outpatient setting with a home setting may be a stronger and clearer example for when usability testing should be done.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised. Refer to comment 609.</p>
602	L446-459	9	<p>Comment:</p> <p>Usability and human factors studies are not clinical studies, so the more appropriate location for this information is Module 3.2.R not in Module 5.</p> <p>Proposed Changed Text</p> <p><i>detailed information on usability and human factors studies (or justification for their absence) should be presented in Module 5, and a summary should be provided in Module 3.2.R (cross referencing the detailed study in Module 5)</i></p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised. Refer to comment 609.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<u>A summary of usability and human factors studies should be presented in Module 3, while cross-referencing the detailed study provided in Module 3.2.R.</u>	
603	L450-453	31	<p><u>Comment:</u></p> <p>“Detailed information on usability and human factors studies... should be presented in Module 5, and a summary should be provided in Module 3.2 (Cross-referencing the detailed study in Module 5).”</p> <p>Recommend including usability and human factor studies in Module 3. Usability and human factor studies are not clinical studies, so the more appropriate location for this information seems Module 3.2. Alternately, suggest this information may be provided in Module 3.2 and cross-referenced in Module 5 to Module 3.</p>	<p>The comment is acknowledged.</p> <p>Refer to comments 602 and 609.</p>
604	L451-453	14	<p><u>Comment:</u></p> <p>Usability and human factors are often not clinical studies, and so would sit better in Module 3, cross-referenced from Module 5 if needed if clinical studies are performed.</p> <p><u>Proposed change:</u></p> <p>Revise to state Module 3 cross-reference should be to Module 5 if it is required</p>	<p>The comment is acknowledged.</p> <p>Refer to comments 602 and 609.</p>
605	L452	19	<p><u>Comment:</u></p> <p>Refer to comments to 184-187, above.</p>	<p>The comments are acknowledged.</p> <p>Text relating to ATMPs has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
606	L455 and L567	14	<p>Comment:</p> <p>The disclaimer “where evidence of usability is required” misses a criterion by which to judge when “evidence of usability” is / is not required.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised. Refer to comment 609.</p>
607	L457	14	<p>Comment:</p> <p>Should be clear that the usability study demonstrates the usability of the DDC not of the medicinal product.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised. Refer to comment 609.</p>
608	L459	14	<p>Comment:</p> <p>Use EN harmonized standards references</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
609	L446-459	14	<p>Comment:</p> <p>This section is not altogether clear. The comments are consolidated into one proposal below.</p> <p>Proposed change:</p> <p>Revise as follows:</p> <p>In case the usability tests (human factors studies) have been evaluated by the Notified Body, it will be sufficient to present a human Factors engineering summary study summary should be presented in Module 3.</p> <p>“If the devices has not been used in the proposed patient population by the intended user population before or if other aspects of the intended use, including changes to the user population or setting of use_z is new and different from the intended use as confirmed by the certificate of conformity or NBOp (e.g. a prefilled syringe used for the first time in an outpatient a home setting or</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>used for the first time in by patients with conditions which could impair use), a usability study – to evaluate whether the DDC can be used safely and effectively to deliver the medicinal product to the target patient population - is expected.</p> <p>In this case and in cases where no Notified Body opinion is needed (devices classified as class I if used separately), detailed information on use-related risks and results of usability and human factors studies (or justification for their absence) should be presented in Module 5, and a summary should be provided in Module 3 (cross-referencing the detailed study in Module 5 if relevant).</p> <p>In all other circumstances, a study summary should be presented in 3.2.R. This is considered a multidisciplinary topic and will also be reviewed outside of quality considerations."</p> <p>"Where evidence of usability adequacy of the device user interface is required, this may be supported by published and/or other relevant data for identical/similar devices on the market.</p> <p>However, if usability this adequacy cannot be satisfactorily demonstrated in this way, a formal usability study is required to demonstrate usability safe and effective use of the DDC medicinal product by the intended user population(s). Applicants are encouraged to follow/use relevant harmonised standards to demonstrate compliance such as EN 62366-1:2015 and IEC/TR 62366-2:2016."</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>6. NON-INTEGRAL DDCs (L463-475)</u>				
610	L463	9	<p><u>Comment:</u></p> <p>Please, consider the event that the manufacturer of the drug product and the manufacturer of the device are not the same and that the two components of the DDC have not been co-developed (with the exception of the data generated on the combination in order to demonstrate the quality, safety and efficacy of the drug product when administered through the referenced device). In the case the manufacturers of the DDC components are not the same, it could be difficult for the drug product manufacturer to retrieve detailed and specific info about the device (e.g. mechanical functionality of the device) because of not disclosable proprietary information. Please, consider the possibility for the drug manufacturer to cover the device requirements (apart from providing evidence of quality, safety and efficacy of the drug-device combination) with the reference to the Declaration of Conformity issued by the device manufacturer or to the NB Certificate of Conformity.</p>	<p>The comment is acknowledged.</p> <p>The text is not changed because the guideline does not require the provision of this data.</p>
611	L463	14	<p><u>Comment:</u></p> <p>GQR should explicitly stipulate that Non-Integral combination products would fall into Directive 2001/83/EC or Regulation (EC) No 726/2004</p>	<p>The comment is acknowledged. Reference is made to the scope of the guideline.</p>
612	L463 and L546	27	<p><u>Comment:</u></p> <p>EFA would like to highlight the need to address the issue of waste of devices in the context of non-integral DDCs. For example, the package of dry-powder inhalers to treat asthma</p>	<p>The comment is acknowledged.</p> <p>The issue regarding waste is out of scope of the guideline.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>typically includes the medicine-containing canister, and the mouthpiece, likely made of hard plastic. However, many non-integral DDCs used in respiratory disease are not sold alone, obliging patients not only to buy the whole set every single time they need the medicine, but also discarding a used mouthpiece that could be reused for a longer period of time. This, of course, requires clear and simple instructions on how to clean the device, but also the option to obtain a new device separately if the old one breaks down (see below). To avoid unnecessary waste, EFA recommends EMA to introduce waste-management considerations in the MAA, looking in particular into several points:</p> <ul style="list-style-type: none"> ▪ The commercialisation of canisters separately (provided the development of agreements that make canisters eligible for reimbursement by national insurance schemes) ▪ Information on the usability period of a mouth-piece ▪ Clear instructions for the maintenance and sterilization of DDCs components to ensure safe re-use ▪ Information and waste disposal systems for discarded DDCs. ▪ Information on the recyclability and carbon footprint impact of the device, including the environmental burden of the drug delivery system 	
613	L466	14	<u>Comment:</u>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>In exceptional circumstances does not align with the scope itself.</p> <p><u>Proposed change:</u></p> <p>Exceptional circumstances needs to be explained, or revised to align with scope language</p>	
614	L466	10	<p><u>Comment:</u></p> <p>Please provide examples of medical devices that is covered under 'exceptional cases'.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
615	L466	18	<p><u>Comment:</u></p> <p>It is not clear if the statement "in exceptional cases" infers that the practise of cross-labelling the use of a device with a particular medicinal product is a rare event or if this statement means that the practise of cross-labelling is to be discouraged</p> <p><u>Proposed change:</u></p> <p>Remove the phrase "in exceptional cases" or if cross-labelling is not acceptable provide a clear statement of intent.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
616	L467	22	<p><u>Comment:</u></p> <p>As described in our comments to line 81 - 87 above, PDA strongly suggests revising the phrase "specific type of administration device" to provide clarity</p> <p><u>Proposed change:</u></p> <p>... in exceptional cases, where the use of a one specific finished medical device, identified by brand and type, type of administration device is specifically provided for in</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			the Product Information to ensure the safe and effective delivery of the medicinal product, additional information may need...	
617	L468-470	19	Repetitive to 160-161.	The comment is acknowledged. The text has been revised.
618	L471-475	19	<p><u>Comment:</u></p> <p>The specificity of the Intended Use is another factor that should influence the inclusion of further information. There is always the potential that the device developer and/or Notified Body did not anticipate the particular intended use to which the applicant wishes to put the device, when developing/reviewing.</p> <p>In my experience, it is very easy to simply refer to the description on a CE-certificate as a surrogate for a documented Intended Use statement. This is not in my opinion not an adequate check.</p> <p><u>Proposed change:</u></p> <p>EMA could use this opportunity to require that an Intended Use statement from the device manufacturer is provided alongside the CE-certificate. This should not be a burden for the industry where such exist. Where no such document exists, this can be the basis for further pharma and/or agency scrutiny on the appropriateness of the device for the proposed application.</p>	The comment is acknowledged. Text in this section has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.1. MODULE 1, PRODUCT INFORMATION (L476-494)</u>				
619	L476	14	<p>Comment:</p> <p>'Co-packed' is used while in the rest of the text 'co-packaged' is used.</p> <p>Proposed change:</p> <p>"6.1. Non-Integral DDCs with co-packed co-packaged medical devices"</p>	<p>The comment is acknowledged.</p> <p>Consistent terminology is now used.</p>
620	L476	14	<p>Comment:</p> <p>It is not clear whether this title refers to a non-integrated product being supplied with an additional co-packed medical device; or whether this is intended to mean that the overall product is non-integral and incorporates a co-packed element. There are examples of products that are both integrated and co-packed e.g. a luer-lock pre-filled syringe with a co-packed injection needle; whilst there are also examples of products that are non-integral and co-packed e.g. a reusable injection pen provided with drug-filled cartridges and co-packed injection needles.</p> <p>Proposed change:</p> <p>Re-word the title to be specific to the intended case.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
621	L476	19	<p>Comment:</p> <p>It is not clear whether this title refers to a non-integrated product being supplied with an additional co-packed medical device; or whether this is intended to mean that the overall product is non-integral and incorporates a co-packed</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>element. There are examples of products that are both integrated and co-packed e.g. a luer-lok pre-filled syringe with a co-packed injection needle; whilst there are also examples of products that are non-integral and co-packed e.g. a reusable injection pen provided with drug-filled cartridges and co-packed injection needles.</p> <p><u>Proposed change:</u></p> <p>Re-word the title to be specific to the intended case.</p>	
622	L477	14	<p><u>Comment:</u></p> <p>See previous SmPC section, line 206, same points apply here.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
623	L478-480	14	<p><u>Comment:</u></p> <p>We suggest the following change to facilitate the correct use of the device.</p> <p><u>Proposed change:</u></p> <p>Unless otherwise justified, where specific device(s) is (are) necessary for the correct use of a medicinal product and is (are) co-packaged with the medicinal product, the specific device(s) should be defined in the product information in the following sections or included as part of specific subsection describing the device Instructions For Use.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
624	L481-482	28	<p><u>Comment:</u></p> <p>Focus should be on the combination only – cleaning for a device is governed by the device regulation and not pharmaceutical law. Will trigger unnecessary variations</p> <p><u>Proposed change:</u></p> <p>Delete “(including cleaning of the device as necessary)”</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
625	L482	19	<p><u>Comment:</u></p> <p>Refer to both comments to 210, above</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 210.</p>
626	L483	19	<p><u>Comment:</u></p> <p>Refer to 211, above.</p>	<p>The comment is acknowledged.</p> <p>Refer to comment 211.</p>
627	L483	35	<p><u>Comment:</u></p> <p>In the case of a non-integral drug-device combination the in-use shelf-life of the single components may be different. Specify what is meant for “in-use shelf-life” of a non-integral combination and how to determine it.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
628	L484	14	<p><u>Comment:</u></p> <p>The storage condition for the non-integral device that is supplied as co-packaged should be based on the more stringent storage condition of the medicinal product since the device should not complicate the storage to facilitate patient or HCP usage.</p> <p>The guidance should clarify that this should be a single storage condition applicable to the medicinal product as well as the device part of the co-package. Unless there are special storage conditions different from the storage</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			conditions associated with the medicinal product, which need to be specified.	
629	L485	14, 31	<p><u>Comment:</u></p> <p>As the co-packed device is CE-marked – relevant device information is included in the device IFU. Additional information can be included in the SmPC at the discretion of the MAH. Information on component materials is difficult to obtain/maintain as the information is held by the device manufacturer and placed in the technical file, unless the device component is made up of a particular component material which has been associated with health risks.</p> <p><u>Proposed change:</u></p> <p>Delete “and its (their) component material(s)”</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
630	L485	3	<p><u>Comment:</u></p> <p>According to our understanding for non-integral DDCs a high-level description of the device and components/ materials should be acceptable rather than providing detailed information on each component. E.g. ‘...the device is made of plastic materials (ABS)...’ rather than specifying the exact grade of polymer including trade name.</p> <p>This would also be in line with the requirements for P.7 (lines 537-539)</p> <p><u>Proposed change:</u></p> <p>None - point for clarification only.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
631	L485	14	<p><u>Comment:</u> There is a reference here to “type of device”.</p> <p><u>Proposed change:</u> Under the MDR, device types will be indicated by their medical device nomenclature (i.e. CND code). It would improve consistency between EMA and NBs if the device code was used in both places, especially for market surveillance purposes.</p>	<p>The comment is acknowledged. Text in this section has been revised.</p>
632	L485	19	<p><u>Comment:</u> Refer to 214-215, above.</p>	<p>The comment is acknowledged. Refer to comments 214 and 215.</p>
633	L485	24	<p><u>Comment:</u> ...and its (their) component material(s) should be listed.</p> <p><u>Proposed change:</u> Delete.</p>	<p>The comment is acknowledged. Text in this section has been revised.</p>
634	L485	28	<p><u>Comment:</u> See comment to line 213.</p>	<p>The comment is acknowledged. Refer to comment on L213</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
635	L487	2	<p>SmPC section on preparation or handling</p> <p><u>Comments:</u></p> <ul style="list-style-type: none"> - There are some inhalers that need a lot of strength to make it work – this is problematic for older and frail people - The loss of functional stability needs to be checked regularly because bad use or bad cleaning of the inhaler can lead to a broken inhaler <p><u>Proposed change:</u></p> <ul style="list-style-type: none"> - User friendly inhalers <p>It needs to be easy to clean the inhaler (dishwasher?) and also to obtain a new one separately if the old one broke down</p>	<p>The comment is acknowledged.</p> <p>Case specific considerations are outside of the scope of this guideline.</p>
636	L488	5	<p><u>Comment:</u></p> <p>Does the device still require an IFU? The GSPRs say yes but is contradicts line 223.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
637	L488	28	<p><u>Comment:</u></p> <p>Guidance is too restrictive and does not adequately adopt user orientation of Human Factors Engineering of DDCs</p> <p><u>Proposed change:</u></p> <p>Edit to read:</p> <p>Information should be consistent with the SmPC, provide clear and simple user-oriented instructions on the intended use of the DDC for the patients and/or for healthcare professionals and be written in such a way as to prevent medication errors.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
638	L488-491	18	<p><u>Comment:</u></p> <p>From the details provided in this paragraph, it appears that the package leaflet will need to duplicate some information from the IFU rather than provide within the pack a copy of the IFU. There is a danger that information relating to the device could be lost by this approach and information such as the device manufacturer, EU Authorised Representative and NB involved in the conformity assessment process may be lost by this approach.</p> <p>As the device in this non-integral configuration is CE-marked then the labelling requirements for the device component shall need to be in conformance with the MDR Annex I, Chapter III GSPRs, which does not seem to have been addressed or considered by this Guideline.</p> <p><u>Proposed change:</u></p> <p>For a non-integral co-packaged device, the device itself will be CE-marked and an Instruction for use (IFU) (if available) should be included in the secondary package.</p> <p>The outer packaging should list the components of the pack including reference to the medical device, the manufacturer of the device and NB number for the NB involved in the conformity assessment</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
639	L488-491	19	<p>Comment:</p> <p>It is not clear whether EMA are suggesting that for non-integral DDCs it is mandatory to integrate the PIL and IFU, or whether this is optional.</p> <p>Additionally, the requirement for inclusion of a standalone device's IFU with the finished combined product is not clear. There are normally several options available, including:</p> <ul style="list-style-type: none"> - direct inclusion in addition to the PIL (potential for confusion and frustration with multiple leaflets) - integration of device IFU content into PIL (potential for restructuring/changes to a validated device IFU, conflict with Medical Device legislation) - PIL reference to where a user may find the device IFU e.g. website (potential for un-informed use/use error) <p>In my opinion, a combiner must ensure to incorporate the full device instructions with the finished product. Changes to the device IFU must be appropriately managed to ensure transfer of up-to-date information to subsequent users.</p> <p>Proposed change:</p> <p>Clarify these points via suitable language.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
640	L488-491	19	<p>Comment:</p> <p>Refer to 216-218, 220, and 217, above</p>	<p>The comment is acknowledged.</p> <p>Refer to comments 216-218 and 220.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
641	L488-494		<p>Comment:</p> <p>It should be very clear that in all cases for a medicinal product the medicinal directives takes precedence. This should also be specifically defined for Annex 1 point 23.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
642	L488-494 (see comment L216-225)	14	<p>Comment:</p> <p>Further clarity is requested regarding how to handle a device part of the non-integral DDC which does not have sufficient space for the CE mark on (as per Article 20 MDR the CE mark would have to be placed on the packaging): should the CE mark be included in the DDC PIL?</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
643	L490-491	8	<p>Comment:</p> <p>We assume the information provided by the IFU should be transferred as verbatim and as complete as possible, because the IFU consolidates many requirements stipulated by the Medical Device Regulation (Regulation (EU) 2017/745), which could be seen differently from assessors of pharmaceutical products. However, it shouldn't be made to simple to change the wording just due to the fact that the device is sold as a Drug-Device combination product. Therefore, the wording "<i>if applicable</i>" doesn't seem to convey the right attentiveness in the processing of this kind of information. We would recommend to replace those words by "<i>as far as possible</i>".</p> <p>Proposed change:</p> <p>Information related to the use of the device, consistent with the device IFU, if applicable as far as possible, should be included.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
644	L492	3	<p><u>Comment:</u> Subheading says "Package leaflet and labels", but the text is referring to outer packaging and package leaflet.</p> <p><u>Proposed change:</u> Change subheading to "Package leaflet and labelling". Information in line 488 to 491 could be included under this subheading as well, as it refers to the package leaflet</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
645	L492	5	<p><u>Comment:</u> Again, need to clarify labelling follows 2001/83 not MDR.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
646	L492	22	<p><u>Comment:</u> In the description of "package leaflet and labels" for non-integral DDCs, it is currently not clear how a manufacturer would label a co-packaged device to avoid confusion. It is assumed that the outer packaging would contain reference to the DDC only to avoid confusion for the end user but this is not clear from the current text of the guidance.</p> <p><u>Proposed change:</u> PDA suggests that EMA include text here similar to the text provided on lines 223-225 for integral DDCs.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
647	L492-494	35	<p>Comment:</p> <p>It is not clear if it is possible/mandatory to include in the leaflet of a non-integral drug-device combination information and symbols referred to the device component as per the requirements set out in the General Safety and Performance Requirements (GSPRs). If the manufacturer does not include information and symbols for the device part, theoretically the GSPRs won't be satisfied leading to the lack of possibility to apply the CE mark. Please clarify the expected contents for the outer packaging and package leaflet for the device component of a non-integral combination.</p>	<p>The comment is acknowledged.</p> <p>Text in this section has been revised.</p>
<p><u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.2. MODULE 3.2.P.1 DESCRIPTION AND COMPOSITION (L496-497)</u></p>				
648	L497, 508	14	<p>Comment:</p> <p>In P.1, "function" of the device must be provided; in P.2, "functionality" of the device must be provided. Clarify each of the two terms and in case they encompass the same, avoid the redundancy by selecting a single section where this information is expected to be provided.</p>	<p>The comment is acknowledged.</p> <p>Text has been revised.</p>
<p><u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.2. MODULE 3.2.P.2 PHARMACEUTICAL DEVELOPMENT (L498-535)</u></p>				
649	L499-500	8	<p>Clarification seems to be necessary concerning the wording: "<i>It is expected that the use of a medicinal product with a specified device is demonstrated to be safe and effective.</i>", because the guideline explicitly applies also to Drug Device combinations, where the device is obtained separately.</p>	<p>The comment is acknowledged. Refer to Section 6.2 for requirements regarding separately obtained devices.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>The current wording may lead to the impression, that each injectable product (even when it is presented in a multiple-dose vial with rubber stopper) needs to mention in future a specific syringe or injection system in the Product Information with the consequence to provide further data on the recommended device.</p> <p>This understanding would lead to highly undesired specificity on the market regarding syringes, needles and pharmaceutical products. Because in accordance with this guideline, such combinations can be considered as non-integral combination products, too. We suggest that the author of this draft guidance would like to emphasise, that additional data according this guideline are required, where a specific device is mentioned in the Product Information, where it is anticipated, that the performance parameter of the device may substantially impact the quality, safety and/or efficacy of the whole combination product.</p>	
650	L499-510	23	<p>Applicants should avoid, or justify through proactive risk assessments, choosing a non-integral, and therefore mass-produced, dosing device unrelated to the medicinal product. EMA must refuse all marketing authorisation or variation applications when a dosing device is needed but not provided.</p>	<p>The comment is noted. As explained in the guideline, Applicants are required to justify the suitability of a medical device to be used in combination with a particular medicinal product.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
651	L502	14	<p>Comment: The term “evidence of suitability” seems redundantly covered in later sections under sub-groups such as “functional aspects” (line 516), sterility (l. 523), compatibility (l. 526) etc. that all contribute to “evidence of suitability”. Clarify what is expected to be provided in P.2 as far as “evidence for the suitability” is concerned.</p>	The comment is acknowledged. The text has been amended.
652	L502-504	14	<p>Comment: If the device is CE-marked the development data should have been reviewed and approved to a NB already and approved by a CA if applicable., therefore it is not clear as to why pharma companies need to repeat what has been done here?</p> <p>Proposed change (if any): Development data should be reviewed only by the NB.</p>	The comment is acknowledged. Relevant development data is required to be included in the dossier.
653	L502-505	9	<p>Comment</p> <p>The change proposed below aims to clarify that the “clear narrative description” of the device is only required for the aspects related to the development of the combination with the drug (i.e. the description of device development itself is not required)</p> <p>Proposed Changed Text</p> <p><i>This section should provide evidence for the suitability of the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product development intended as a combination, and provide all relevant data (including justification of any new device, pharmaceutical form or excipient, etc., not previously used, where relevant).</i></p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
654	L502-505	24	<p><i>Comment/ Quote</i></p> <p>"This section should provide evidence for the suitability of the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product development, and provide all relevant data (including justification of any new device, pharmaceutical form or excipient, etc., not previously used, where relevant)."</p> <p><i>Proposed change (if any):</i></p> <p>Delete this sentence since this information is not relevant and will not be available to the MAH.</p>	The comment is acknowledged. The text has been amended.
655	L504	19	<p>Comment: Refer to 232-236, above.</p>	The comment is acknowledged. The text has been amended.
656	L505-507	19	<p>Comment: The text regarding risk-based inclusion of information should also apply to integral products.</p> <p>Proposed change (if any): Incorporate similar text to 231-242</p>	The comment is acknowledged. The text has been amended.
657	L505-507	14	<p>Comment: A rationale should be included here rather than simply quoted text</p> <p>Proposed change (if any): Please could the agency be more precise within this paragraph and link it with MDR device classification?</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
658	L511-512	14	<p>Comment: It is not clear why the basic structure of the CTD is being deviated from. P.2.1 is meant to discuss DS and excipients – P.1 already provides the description of the Device so propose not to have any repeat info in P.2.1.</p> <p>Proposed change (if any): Delete the following: P.2.1 Components of the Drug Product A high-level description of the devices(s)/DDC should be provided.</p>	The comment is acknowledged. The text has been amended.
659	L512	6	Delete 'high-level'	The comment is acknowledged. The text has been amended.
660	L513-515	27	The usability of the drug product vis-à-vis the device in non-integral DDCs is another example of a discussion where patients can offer their experience-based input. EFA believes that EMA should offer clear statements towards this direction, ensuring patients' involvement.	The comment is acknowledged. This is out of scope of the guideline
661	L514	14	<p>Comment: The phrase "intended use (usability)" suggests these two things are synonymous.</p> <p>Proposed change (if any): Revise as follows: "...be provided, referring to the intended use and the rationale for the choice (e.g., usability, rationale for choice of device, adequacy of device for the user population, drug characteristics, etc.).</p>	The comment is acknowledged. The text has been amended.
662	L514-521	14	<p>Comment: It is not clear why the basic structure of the CTD is being deviated from. P.2.2 is not meant to discuss any device issues – propose to move all device info under P.2.2 to P.2.6 as this is in line with ICH M4Q for non-integral devices: "The compatibility of the drug product with</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling".</p> <p>Proposed change (if any): Move lines 514-521 to sit just above line 527 under P.2.6 heading.</p>	
663	L515	2	<p>The usability of the drug product</p> <p><i>Comments</i></p> <p>Can be complicated in the Dutch system with the preference policy because agreements are made in regions about the preferred inhalers to avoid too much choice. Also, some health insurance company only reimburse a limited set of inhalers.</p>	The comment is acknowledged. This is out of scope of the guideline.
664	L516	19	<p>Comment: Statement regarding qualification in line with complexity should be equally applicable to integral products.</p> <p>Proposed change (if any): Incorporate similar text to 246-253.</p>	The comment is acknowledged. The text has been amended.
665	L518-519	19	<p>Comment: Statement regarding dose delivery performance being demonstrated with the intended medicinal product should be equally applicable to integral products.</p> <p>Proposed change (if any): Incorporate similar text to 246-253.</p>	The comment is acknowledged. The text has been amended.
666	L518-519	14	<p>Comment: Wording of requirements varies and should be aligned. It is recommended to use the wording of line 501.</p>	The comment is acknowledged. No change is made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): It should be demonstrated that the device is able to deliver the required dose of the medicinal product accurately and reproducibility within the intended use.	
667	L519-520	23	Dosing devices must be fit for purpose and accurate. They should have no superfluous markings/graduations. They should be marked with the medicinal product's trade name and International Non-proprietary Name and, where necessary, its strength or the age range of the patients for which it is intended (e.g. <i>levetiracetam</i>).	The comment is acknowledged. As explained in the guideline, Applicants are required to justify the suitability of a medical device to be used in combination with a particular medicinal product.
668	L520-521	14	Comment: with other relevant handling information in section 6.6	The comment is acknowledged. The text has been amended.
669	L520-521	28	Comment: Remove (as for lines 481-482)	The comment is acknowledged. The text has been amended.
670	L522-525	18	<p>Comment: The requirement to verify the sterility of the non-integral device is not clear and it is not appropriate to state that verification can be by the reference to a CE Certificate as the applicability of sterility depends on the Certificate scope.</p> <p>Additionally, as a non-integral device the device itself should be CE certified, with the device sterility provided in the final DDC package in its primary packaging, the integrity of which is key to assurance of sterility.</p> <p>Proposed change (if any):</p> <p><i>For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate) is assumed, so long as the</i></p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<i>device is supplied in its primary packaging with the sterile barrier intact.</i> Maintenance of sterility throughout use and shelf-life of the final medicinal product should also be demonstrated.	
671	L523	28	Comment: In-consistency Proposed change (if any): Edit to read: "... non-integral device..." → "non-integral DDC"	The comment is acknowledged. The text has been amended.
672	L523-525	9	<u>Comment - CRITICAL</u> For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate). In-use safety after opening should be assessed. For example, a sterile drug product to be administered via inhalation with a dedicated nebulizer cannot maintain the sterility once the container closure system is opened, both in a domestic as well as in the hospital environment. <u>Proposed Changed Text</u> <i>For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate). Maintenance of sterility throughout use and shelf-life of the final medicinal product should also be demonstrated.</i>	The comment is acknowledged. The text has been amended.
673	L524-525	10	Clarification of the expected data requirements in relation to "maintenance of sterility throughout use and shelf-life of the final medicinal product" for non-integral DDCs obtained separately would be helpful.	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
674	L524-525	14	<p>A demonstration is asked for maintenance of sterility (of the device) through use and shelf life of the medicinal product.</p> <p>Here, it should instead be sufficient to explain that the CE marked device will be used within the shelf life assigned by its legal manufacturer, without any further demonstration of sterility maintenance.</p>	The comment is acknowledged. The text has been amended.
675	L524-525 and L527-528	20	<p>Comment: Our comment above on lines 376-377 also applies to these statements.</p> <p>Proposed change (if any): State definitively whether or not extrapolation of stability data may be acceptable when establishing the shelf life or retest date for a DDC, depending upon the specific characteristics of the product.</p>	The comment is acknowledged. The text has been amended.
676	L525	14	<p>It is mentioned that demonstration of maintenance of sterility throughout use and shelf-life of the final medicinal product should be provided in P2.5. Use of cross-reference to stability sections should be made possible to avoid redundancy of information across the dossier.</p>	The comment is acknowledged. This is covered under Section 4.2.
677	L526-535	14	<p>Comment: Non-integral /co-packed devices are by definition not in contact with drug product during the storage and shelf-life.</p> <p>Proposed change (if any): Rationalise this section to focus only on (transient) drug to device interactions at point of use.</p>	The comment is acknowledged. The text has been amended.
678	L526-535	19	<p>Comment: Non-integral /co-packed devices are by definition not in contact with drug product during the storage and shelf-life.</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed change (if any): Rationalise this section to focus only on (transient) drug to device interactions at point of use.	
679	L529 and L544	14	Comment: In two locations, it is expected that in-use stability be presented. Such redundancy should be avoided.	The comment is acknowledged. No change is made.
680	L529-533 and L544-546	10	<p>Comment: The guidance appears to recommend inclusion of in-use stability data as part of both P.2.6 and P.8 for non-integrated DDCs with co-packed medical devices</p> <p>Proposed change:</p> <p>Provide a single location for in-use stability data. Consider to recommend section P.8 to be consistent with the location recommended for in-use studies for integral DDCs.</p>	The comment is acknowledged. No change is made.
681	L532	14	<p>Comment: The document states that “interaction studies” should be performed using a risk-based approach.</p> <p>The delivery devices that we typically use for an oral solution / syrup are made of plastic. It would be great to receive confirmation that the principles of the EMA guideline on Plastic primary packaging materials (CPMP/QWP/4359/03) apply to determine whether or not interaction/leachables studies are needed.</p> <p>Proposed change (if any):</p> <p>please confirm applying guidelines can be part of the risk management</p>	The comment is acknowledged. This is out of scope of the guideline.
<u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.2. MODULE 3.2.P.7 CONTAINER CLOSURE SYSTEM (L536-542)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
682	L537-542	11	<p>Proposed changes:</p> <p>Inclusion of the following sentence:</p> <p>"If the non-integral DDC becomes part of the container closure system (for example a drug transfer device attached to a vial) the device should prevent microbial ingress and maintain the sterility of the medicinal product throughout its use."</p>	The comment is acknowledged. The text has been amended.
683	L537-542	24	<p><i>Comment</i></p> <p>This section describes GMP-relevant issues. It is not relevant for regulatory affairs and the dossier.</p> <p>Information should be stated in quality agreements with the manufacturer of the device.</p> <p><i>Proposed change</i></p> <p>Delete.</p>	The comment is acknowledged. No change is made.
684	L539-541	14	<p>Comment: It deems to be no added value to provide the specification applied to the incoming delivery device as the PQS of the organization will ensure the respective evaluation is conducted. Recommended to delete this requirement of the dossier.</p>	The comment is acknowledged. The text has been amended.
685	L539-541	28	<p>Comment:</p> <p>"The specification applied to the incoming device upon receipt by the drug product manufacturer should be presented." Needs to be rephrased to something more high level, as otherwise any change to specification could trigger a drug variation which is ineffective and unnecessary.</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any):</p> <p>Identification of the incoming device upon receipt by the drug product manufacturer should be presented.</p>	
686	L540	14	<p>Comment: It does not seem relevant to incorporate incoming goods specification details for a co-packed device into the container closure section of the dossier.</p> <p>This is typically handled as a bought-in item for inclusion during the final packaging steps of the manufacturing process. It would seem more appropriate to incorporate such information into either manufacturing content or 3.2.R.</p> <p>The specification should be restricted to any product-contacting fluid flow components of the device.</p> <p>Proposed change: "The specification applied to the incoming device product-contacted components, upon receipt by the drug product manufacturer should be presented."</p>	The comment is acknowledged. The text has been amended.
687	L540	19	<p>Comment: It does not seem relevant to incorporate incoming goods specification details for a co-packed device into the container closure section of the dossier. This is typically handled as a bought-in item for inclusion during the final packaging steps of the manufacturing process. It would seem more appropriate to incorporate such information into either manufacturing content or 3.2.R.</p>	The comment is acknowledged. The text has been amended.
<u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.2. MODULE 3.2.P.8 STABILITY (L543-546)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
688	L543-546	27	<p>Comment:</p> <p>EFA holds that the design of medical devices and/or components should in no case create any additional non-health burden to the patient resulting from their use. A specific case at hand is the (non-)electrostatic inhaling chambers, a key component of Metered Dosing Inhalers that are used in the management of respiratory diseases such as asthma. As opposed to non-electrostatic, the electrostatic ones typically require considerable cleaning after each use, creating a daily burden to users. At EFA we believe that the DDCs maintenance factors are issues that also need to be assessed in the quality requirements, and resolved through patient-centred actions in the product design process.</p> <p>Furthermore, the device needs to be robust so that cleaning should not lead to an impairment. For example, when washed in the machine, some chambers might have their rubber parts broken down, at the risk of being inhaled.</p> <p>Finally, throughout the process of product design, pharmaceutical companies should be knowledgeable of and compliant to national particularities for specific DDCs. For example, in some countries several DDCs are identified with a particular colour, clearly distinguishing them from another type or sub-type of the product. Lack of compliance to such a national practice might cause confusion to the patients, urging them to purchase the wrong product for the management of their disease. For example, there was an issue with a GSK inhaler that was produced in the wrong colour. Patients in some countries e.g. UK and Netherlands consider blue inhalers as bronchodilator and red inhalers as maintenance inhalers.</p>	The comment is acknowledged. Cleaning has been taken into consideration; other aspects are out of scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>GSK developed a blue maintenance inhaler which led to many problems. GSK therefore changed the colour of the inhaler.</p> <p>Proposed change (if any): DDCs like aero chambers should be designed in a way that makes swallowing the cap impossible. Moreover, the use of inhalers needs to be intuitive.</p>	
689	L544	19	Comment: Refer to 526-535, above.	The comment is acknowledged. The text has been amended.
690	L544-546	14	<p>Comment: It is not clear how 'in use' testing is different to the 'functionality tests'. The functionality testing, through shelf-life, should be performed under 'in use' conditions. Any 'in use' stability that is not part of the formal stability program and performed once to qualify the DDC would be in 3.2.P.2.6 or 3.2.R.</p> <p>Proposed change: "If relevant, in-use functionality stability data should be provided under in-use conditions for the drug product in contact with the device, including device functionality that may impact the quality, safety and/or efficacy of the medicinal product."</p>	The comment is acknowledged. No change is made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
691	L546	2	<p>Design of medical inhalers and/or components</p> <p><i>Comment:</i></p> <ul style="list-style-type: none"> - Sometimes rubbers from aero chambers break during cleaning <p><i>Proposed change (if any):</i></p> <ul style="list-style-type: none"> - Swallowing the cap should be impossible. Some patients forget to take it off – do they need a hole in the top like pen lids? - The use of inhalers needs to be intuitive <p>Inhaler needs to be robust. So, cleaning should not lead to an impairment.</p>	The comment is acknowledged. Cleaning has been taken into consideration; other aspects are out of scope of the guideline.
<u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.3. MODULE 3.2.A.2. ADVENTITIOUS SAFETY EVALUATION (L547-549)</u>				
692	L548 – 549	14	<p>Comment: It is not clear by when the Certificate of Conformity is not valid anymore</p> <p>Proposed change: Clarify that the certificate is a one-time only request that only needs updating when there is a significant change in the device constituent.</p>	The comment is acknowledged. The text has been amended.
693	L548-549	14	<p>Comment: “Self-declared” presumably refers to the availability of a declaration of conformity for a Class I device, and absence of a NB certificate of Conformity.</p> <p>It is unclear why the manufacturer's declaration of conformity is not sufficient evidence for compliance of the device with EU requirements for adventitious agent safety.</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
694	L548-549	18	<p>Comment: A medical device that is manufactured utilising materials (non-viable) of human or animal origin would be classified as a Class III medical device in accordance with MDR, Annex VIII, Rule 18 and therefore reference to a self-declared device is not applicable.</p> <p>Proposed change (if any):</p> <p>Remove reference to self-declared devices.</p> <p>If self-declared, the requirements for 3.2.A.2 as for the integral DDCs should be followed with a valid NB CE Certificate of Conformity can be accepted as evidence of compliance with EU requirements.</p>	The comment is acknowledged. The text has been amended to clarify that an EU certificate or EU Declaration of Conformity can be accepted as evidence of compliance of the device (part) with EU requirements.
<u>6.1 NON-INTEGRAL DDCs WITH CO-PACKAGED MEDICAL DEVICES – 6.1.4. MODULE 3.2.R. REGIONAL INFORMATION, MEDICAL DEVICE (L550-574)</u>				
695	L550	9	Include subheadings, to align with equivalent information provided in section 5.4	The comment is acknowledged. No change is made.
696	L550-555	30	<p>Comment:</p> <p>Drug-device combination products especially Non-integral DDC's have different components which typically include:</p> <ol style="list-style-type: none"> 1. Safety-Needle (Class-IIa) 2. Vial Access device (Class-IIa) 3. Syringe with tip-cap (Class-Is) 4. Plunger-stoppers (Class-Is- if procured sterile) 5. Plunger rod (Class-I) 	The comment is acknowledged. The text has been changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>6. Backstop (Class-I)</p> <p>Does the agency expect the applicant to provide EU declaration of conformity from the device manufacturer (for class I devices) and Notified body Certificate of Conformity for risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) for all the above listed components? Please confirm.</p> <p>If yes, then the below proposed changes are suggested in the guideline for better clarity.</p> <p>If answer is no, then the guidance should mention for which components, EU declaration of conformity/ Notified body declaration of conformity is required.</p> <p>Proposed change:</p> <p>If EU declaration of conformity/ Notified body Certificate of Conformity is required for all the components of a Non-Integral DDC's, then lines 550-555 of the guidance should include the term "device(s)" which denotes all the components of Non-Integral DDC's.</p>	
697	L551	14	Comment: In line with a previous comment, please clarify and include an example of the type of information that would comprise this index.	The comment is acknowledged. The text is changed.
698	L553	14	Comment: Please confirm whether the EU DoC is only required for class I non-sterile, non-measuring medical devices only.	The comment is acknowledged. No change is made.
699	L553-554	18	Comment: An EU Declaration of Conformity issued by the device manufacturer does not provide any evidence of the CE-mark, however it is the manufacturers declaration of	The comment is acknowledged. The text is changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>conformity to applicable requirements and the only available evidence for a Class I, self-declared device</p> <p>Proposed change (if any):</p> <p><i>An EU Declaration of Conformity issued by the device manufacturer should be provided for all devices—as evidence of the CE mark.</i></p> <p><i>For devices of risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) a NB CE Certificate of Conformity should also be provided.</i></p>	
700	L553-555	14	<p>Comment: Typo</p> <p>Proposed change (if any): “an NB” becomes “a NB”</p> <p>“An EU Declaration of Conformity issued by the device manufacturer should be provided as evidence of the CE-mark. For devices of risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) an NB a NB Certificate of Conformity should also be provided.”</p>	The comment is acknowledged. The text is changed.
701	L554	6	What is meant with Class Irsi?	Rsi refers to reusable surgical instruments
702	L556	14	Comment: The CE certificate is an indication that the device has been assessed and complies with the MDR.	The comment is acknowledged. The text is changed.
703	L556	28	<p>Comment: “Significant Change”</p> <p>Guidance is lacking regarding determination of changes that are considered significant.</p> <p>Proposed change (if any): Add:</p>	The comment is acknowledged but in the absence of legal definition for “significant change”, this term has been removed from the guideline

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			When changing constituent parts of the DDC please refer to ISO 20069 regarding guidance on those considerations needed for the manufacturer when a change is planned, implemented and controlled	
704	L556-560	19	<p>Comment: This text refers to non-integral devices with co-packed devices. Such devices must be CE-marked.</p> <p>It is not clear whether EMA are assuming Applicant development of the co-packed medical device alongside the medicinal product; or 'Supplier' changes to the medical device.</p> <p>In the former case, the Applicant would need to obtain a CE-certificate for the co-packed device, prior to submission and include this within the MAA.</p> <p>In the latter case, if a substantial change this would require new CE-certification, also needed within the MAA. If not a substantial change, then the existing CE-certificate would continue to support the intended use and further information should not be required.</p> <p>Proposed change: Clarify expectations for change information.</p>	The comment is acknowledged. The text is changed.
705	L556-561	14	<p>Comment: The impact of device changes on product performance should primarily be described in P.2, since it is part of the development narrative.</p> <p>Proposed change (if any): Move paragraph to section to 'P.2.2 Drug product', for example after line 521.</p>	The comment is acknowledged. The text is changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
706	L556-561	14	Comment: Lines 556 to 561 redundant with section 7.	The comment is acknowledged. The text is changed.
707	L558	14	Comment: The text sounds as if “delivered dose” is a usability factor. Proposed change (if any): Revise as follows: “...the impact on product performance characteristics (e.g. delivered dose, needle penetration force for subcutaneous/intramuscular injection) and on usability factors.”	The comment is acknowledged. The text is changed.
708	L562-564	14	Comment: For an integral DDCs, the guidance indicates to provide bridging information in P.2. Is this an intentional difference for non-integral DDCs to place bridging summaries in 3.2.R? Option for either location could be considered for consistency.	The comment is acknowledged. The text is changed.
709	L562-564	10	Further guidance on the content of the summary could be provided so as to minimize duplication between NB and MAA docs. Current level of detail is limited	The comment is acknowledged. No change is made.
710	L565-570	23	These studies are important: EMA would do well to draw inspiration from the FDA and Health Canada guidelines. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-product-design-minimize-medication-errors-guidance-industry The reports of these studies must be documented in EPARs.	The comment is outside the scope of this guideline. Reference is made to existing EU guidance on risk minimisation and prevention of medication errors.
711	L565-572	28	Comment: As for lines 445-459	The comment is acknowledged. The text is changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
712	L566-567	14	<p>Comment: Unclear wording</p> <p>Proposed change (if any): Revise as follows: "...can be used safely and effectively by the intended users to deliver the required dose to the target patient population..."</p>	The comment is acknowledged. The text is changed.
713	L567-569	14	<p>Comment: This section is unclear.</p> <p>The sentence before mentions a HFS is "expected", then "required", then reduced to "formal study".</p>	The comment is acknowledged. The text is changed.
714	L569, L639 and L640	14	<p>Comment: Formal usability study is mentioned</p> <p>Proposed change (if any): Clarify the difference (if any) between usability studies and HFS</p>	The comment is acknowledged. The text is changed to consistently use the same term.
715	L571	14	<p>Comment: same as line 452</p>	The comment is acknowledged. The text is changed.
716	L571	14	<p>Comment: The text refers to "usability and human factors studies" but this is confusing and not consistent with IEC 62366-1:2015.</p> <p>Proposed change (if any): Use the term "usability studies".</p>	The comment is acknowledged. The text is changed to consistently use the same term.
717	L571	14	<p>Comment: Many CE marked devices are acquired from a separate legal manufacturer. The CE certificate provided by the Legal Manufacturer indicates that Usability is acceptable. This suggests that the MAH must complete Usability studies beyond those completed for CE marking in this case.</p> <p>Please could the agency clarify?</p>	The comment is acknowledged. The text is changed to clarify expectations.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
718	L571-572 (see also L451-453)	14	<p>Comment: Usability and human factors are often not clinical studies, and so would sit better in Module 3, cross-referenced from Module 5 if needed, if clinical studies are performed.</p> <p>Proposed change (if any): Harmonize with wording in section 451 - 453:</p> <p>Detailed information on use-related risks and results of usability and human factors studies (or justification for their absence) should be presented in Module 5. A summary should be provided in Module 3.2.R (cross-referring cross-referencing the detailed study in to Module 5 if relevant).</p>	The comment is acknowledged. The text is changed.
719	L571-572	14	<p>Comment:</p> <p>This would be part of Annex I and therefore of the opinion of the NB.</p>	The comment is acknowledged. The text is changed.
720	L571-572	10	<p>Comment:</p> <p>To minimise changes in the eCTD for multi-country submissions in relation to usability and Human Factor study reports it is proposed that a summary report is provided in Module 3.2.R. It is not considered necessary to specify that a detailed report is provided; the information supplied needs to be sufficient to support the intended use and should be justified by the sponsor.</p> <p>Proposed change (if any):</p> <p>Information on usability and human factors studies (or justification for their absence) should be presented in Module 3.2.R.</p>	The comment is acknowledged. The text is changed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
721	L571-572	31	<p>"Detailed information on usability and human factors studies... should be presented in Module 5. A summary should be provided in Module 3.2.R, cross-referring to Module 5."</p> <p>Recommend including usability and human factor studies in Module 3.</p> <p>Usability and human factor studies are not clinical studies, so the more appropriate location for this information seems Module 3.2. Alternately, suggest this information may be provided in Module 3.2 and cross-referenced in Module 5 to Module 3.</p>	The comment is acknowledged. The text is unchanged.
<u>6.2 NON-INTEGRAL DDCs WITH SEPARATELY OBTAINED DEVICES (L575-594)</u>				
722	L575	14, 31	<p>Comment:</p> <p>Potential scope creep for separately obtained devices. Suggest clarifying that well-established technologies are excluded, e.g. give examples as per list in lines 90-7.</p> <p>Proposed change (if any):</p> <p>Well-established technologies such as injection needles, refillable pens, and pumps for medicinal product delivery are not in scope for the requirements set out in this section.</p>	The comment is acknowledged. The final guideline states that the requirements do not apply where reference is made to a general group of devices (e.g. "using a syringe" or "an infusion line", etc.).

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
723	L575-594	14	<p>Comment:</p> <p>The whole Section 6.2 seems redundant to the elements already presented in Section 6.1 for Non-integral DDCs with co-packed medical devices and could be combined to make less confusing.</p> <p>For instance, the same risk-based approach on the impact of the specific device on the medicinal product is needed whether it is co-packed or separate.</p>	The comment is acknowledged. The level of data requirements between co-packaged and referenced device differ, which is reflected in the final guideline.
724	L575	14	<p>Comment:</p> <p>Section 6.2: this will include a wide variety of devices that could be potentially used under the hospital conditions. In a number of scenarios this will be based on the physician choice. A clarification on the expectation from the MAH to include this information will be welcomed. For example, a-prefilled syringe connected to the automated pump-injector, which may differ in various hospital settings.</p>	The comment is acknowledged. See comment 722.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
725	L576-594	31	<p>Comment:</p> <p>This section does not clarify when or how a “specified device” should be considered and is beyond the scope of the language of Article 117. It is confusing when “specified device” is described in 499-507 for co-packaged devices, or where separately obtained devices would be described by their volume (i.e., disposable syringe, infusion pump, etc.) material properties, or function (e.g., non-protein binding filter) in the SmPC rather than meaning a branded marketed device. Inclusion of this category in this guideline may suggest that at NBOp may be needed for non-branded devices referenced in SmPC but not supplied. Further, the requested information in the guideline may discourage manufactures for listing this information that may optimise the safe use or delivery of the drug product.</p> <p>Proposed change:</p> <p>Consider clarifying whether this category refers to branded devices or generic devices that described by general specifications, or deletion of the entire section.</p>	The comment is acknowledged. See comment 722.
726	L578-579	18	<p>Comment:</p> <p>The inclusion of ATMPs and potential use of a device during surgical procedures for application, implantation or administration of the product should be excluded from this Guideline for the following reasons;</p> <ul style="list-style-type: none"> • ATMPs are excluded from the scope of the document as per section 2 Scope • There is a separate regulation governing ATMPs 	The comment is acknowledged. Reference to ATMPs in that section has been removed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ul style="list-style-type: none"> The guideline sets a precedence for additional assessment requirements of devices used during surgical procedures. The phrase does not indicate that the MA Applicant has specified a particular device to be used in the procedure <p>Proposed change (if any): Remove reference to ATMPs</p>	
727	L580	18	The wording "In exceptional cases" is unclear does this mean that the occurrence of specifying a specific device for use with a medicinal product is rare or does it mean that such a practise is not encouraged and should only be considered in exceptional circumstances?	The comment is acknowledged. Reference to exceptional cases has been removed.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
728	L583-584	19	<p>Comment:</p> <p>The 'risk-based approach' to be used to determine the need for a usability study is not elaborated.</p> <p>A non-integral device will have achieved its CE-mark via a process that SHOULD have reviewed usability data. In principle, further usability study should not be required if the device is being used within its Intended Use. However, it is also recognised that such a process may have been performed against a non-specific Intended Use, that may not adequately trigger considerations/needs for certain users. Equally, an Applicant may have not access to usability data related to a CE-marked device that they choose to co-pack.</p> <p>In my opinion, the Pharma applicant should incorporate these considerations into their approach for determining study need and design. If adequate data is not available, and use-based risk assessment identifies the potential for unacceptable harm (either during normal use or foreseeable misuse per ISO 14971), then that Applicant should perform studies appropriate to adequately resolving these points.</p> <p>Proposed change:</p> <p>Clarify the expectations for the risk based approach to be used.</p>	The comment is acknowledged. Text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
729	L584	19	<p>Comment:</p> <p>There is a clear difference between referencing to the need to use specific devices (e.g. Company A, Type B, 27G, 1/2" needle), versus referring to general group of devices that could be used (e.g. 27G needle). When the choice of device may be left to the user/HCP, conducting usability studies across the full range of potentially sourced devices is likely not feasible and may not provide conclusive evidence of usability.</p> <p>Proposed change (if any):</p> <p>Such devices must also be recognised as either Medical Devices or Device Accessories. This terminology should be used within the text. The requirement for potential HF studies should be limited to where specific device referencing is incorporated into labelling and provided information.</p>	The comment is acknowledged. The text has been revised.
730	L584	14	<p>Comment:</p> <p>There is a clear difference between referencing to the need to use specific devices (e.g. Company A, Type B, 27G, 1/2" needle), versus referring to general group of devices that could be used (e.g. 27G needle). When the choice of device may be left to the user/HCP, conducting usability studies across the full range of potentially sourced devices is likely not feasible and may not provide conclusive evidence of usability.</p> <p>Proposed change (if any):</p> <p>Such devices must also be recognised as either Medical Devices or Device Accessories. This terminology should be used within the text. The requirement for potential HF</p>	The comment is acknowledged. See comment 729.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			studies should be limited to where specific device referencing is incorporated into labelling and provided information.	
731	L585-587	14	<p><u>Comment:</u></p> <p>Sentence is unclear. Bioequivalence implies that two methods of administration are compared. However, the sentence does not state to what other method of administration the administration with "separately obtained device" should be compared.</p>	The comment is acknowledged. The text has been revised.
732	L585-587	14	<p><u>Comment:</u></p> <p>"evidence of efficacy and safety/bioequivalence" for the medicinal product in combination with the device, implies clinical data. We generally agree with this assuming a very specific device/brand/model is referenced in the labelling, however where a specific DDC is not referenced/required it is not possible to clinically test every possible device.</p>	The comment is acknowledged. The text has been revised.
733	L585-586	8	<p>Clarification seems to be necessary concerning the wording: <i>"If a separately obtained device referred to in the product information is used, then there must be evidence of efficacy and safety/bioequivalence for the medicinal product in combination with the device."</i></p> <p>The current wording may lead to the impression, that each injectable product (even when it is presented in a multiple-dose vial with rubber stopper) needs to mention in future a specific syringe or injection system in the Product Information with the consequence to provide further data on the recommended device.</p> <p>This understanding would lead to highly undesired specificity on the market regarding syringes, needles and</p>	The comment is acknowledged. Th text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>pharmaceutical products. Because in accordance with this guideline, such combinations can be considered as non-integral combination products, too. We suggest that the author of this draft guidance would like to emphasise, that additional data according this guideline are required, where a specific device is mentioned in the Product Information, where it is anticipated, that the performance parameter of the device may substantially impact the quality, safety and/or efficacy of the whole combination product.</p>	
734	L585-587	15	<p>Comment:</p> <p>The drafted language ‘If a separately obtained device referred to in the product information is used, then there must be evidence of <i>efficacy and safety/bioequivalence</i> for the medicinal product in combination with the device’ (emphasis added) is too prescriptive given the range of non-integral devices which would be covered by the guideline. Notably, separately obtained devices referenced in an SmPC could be low risk Class I devices, e.g. subcutaneous injection syringes. Laboratory studies encompassing a range of representative devices (and results presented in 3.2.P.2) should be considered adequate to support reference to these devices in the SmPC vs. inferring the need for formal efficacy and/or safety studies in human.</p> <p>Proposed change:</p> <p>‘If a separately obtained device referred to in the product information is used, then there must be <u>adequate evidence of the potential impact to the</u> efficacy and safety/bioequivalence for the medicinal product <u>used</u> in combination with the device.....’</p>	The comment is acknowledged. The text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Alternatively: further clarify the exceptional cases of specific medical devices detailed in SmpC where this applies, expanding on the text in lines 580-582 of the draft guideline.	
735	L588	14	<p><u>Comment:</u></p> <p>For devices obtained separately this may be beyond any reasonable means for control of the MAH.</p>	The comment is acknowledged. The MAH should ensure that any specific devices do no adversely impact the quality, safety and/or efficacy profile of the medicinal product.
736	L592	14	<p><u>Comment:</u></p> <p>In-use stability is typically located in P.2 rather than for the formal stability program.</p> <p><u>Proposed change:</u></p> <p>“In section 3.2.P.8 2, it is expected that in-use stability data are presented, if applicable.”</p>	The comment is acknowledged. Reference to 3.2.P.8 is indeed related to formal stability studies. References to 3.2.P.2. for in-use stability are made for other device categories.
737	L592	14	<p><u>Comment:</u></p> <p>It is not clear how ‘in use’ testing is different to the ‘functionality tests’. The functionality testing, through shelf-life, should be performed under ‘in use’ conditions as stated in the SmPC. Any ‘in use’ stability that is not part of the formal stability program and performed once to qualify the DDC would be in 3.2.P.2 or 3.2.R.</p> <p><u>Proposed change:</u></p> <p>“In section 3.2.P.8, it is expected that in-use functionality stability data, performed under in-use conditions are presented, if applicable.”</p>	See comment 736.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
738	L592	19	<p>Comment:</p> <p>Stability data is not relevant for not provided devices.</p> <p>Proposed change (if any):</p> <p>Remove this sentence or rationalise to focus only on (transient) drug to device interactions at point of use.</p>	The comment is acknowledged. The scope of this section pertains to specific devices, for which in-use stability data is required.
739	L593	14	<p>Comment:</p> <p>The text refers to “usability and human factors studies” but this is confusing and not consistent with IEC 62366-1:2015.</p> <p>Proposed change (if any):</p> <p>Use the term “usability studies”.</p>	The comment is acknowledged. The text has been revised.
740	L593-594	14	<p>Comment:</p> <p>It is not clear why a CE marked, separately obtained device requires information on usability and human factor studies when this is covered by the CE-mark or the outlined information expected for section 3.2.P.2.</p> <p>Proposed change:</p> <p>Delete sentence. Information on usability and human factors studies should be presented, unless otherwise justified (see Section 5.4 above).</p>	The comment is acknowledged. See comment 735.
741	L593-594	28	<p>Comment:</p> <p>As for lines 445-459</p>	The comment is acknowledged. See comment 735.
<u>7. BRIDGING TO DEVICES USED IN CLINICAL DEVELOPMENT (L595-614)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
742	L595-598	10, 24	<p>Line 595 – 598 state: <i>"Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start"</i>.</p> <p>It should be made clear whether a significant change to the design of the medical device part after pivotal clinical trials have been performed is acceptable in case a justification (e.g. bridging study) can be provided that the relevant GSPRs are not impacted/still met.</p>	The comment is acknowledged. The text has been revised.
743	L596-598	8	<p>Comment:</p> <p>Clarification seems to be necessary concerning the wording: <i>"Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start."</i></p> <p>The wording <i>"advanced as possible"</i> is not specific enough, should be changed to <i>"device meets the relevant GSPRs"</i>.</p> <p>However, in cases where the device performance needs to be demonstrated in one clinical setting with an integrated approach of clinical investigations (device) and clinical trial (medicinal product), it is possible that the CE marking still depends on the outcome of the clinical investigation, or the that the CE mark of the device was not granted for the intended purpose for which the device is used in the particular setting.</p>	The comment is acknowledged. See Comment 742.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any):</p> <p><i>"Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start. Exemptions may be granted for those GSPRs which will be proven during an integrated setting of a clinical trial (Medicinal product) and a clinical investigation. In cases of doubt if this approach is justified, it is recommended that an opinion be sought from the responsible CAs."</i></p>	
744	L596 -601	14	<p><u>Comment:</u></p> <p>The statement initially states that the device should be as advanced as possible (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start. Then on line 601 it states that: Integral DDC: there is no requirement for evidence of compliance with the relevant GSPR.</p> <p><u>Proposed change (if any):</u></p> <p>Remove (i.e. meets the relevant GSPRs) from line 598.</p>	The comment is acknowledged. See comment 742.
745	L596-602	35	<p>In line 598 compliance with GSPRs for pivotal clinical studies is required. In line 601 for integral DDC the compliance to the GSPR is not mandatory during previous clinical development but any change with a potential impact on the device quality, safety and efficacy is expected to be described, evaluated and justified in the IMPD for a pivotal clinical study. Is this interpretation correct? Which is the minimum requirement for supporting a development clinical study? Or a pivotal clinical study?</p>	The comment is acknowledged. See comment 742.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
746	L598	9	<p>Comment</p> <p>It is conceivable that device endpoints are included in the pivotal clinical trials especially for drug delivery devices. As such it is possible that not all the GSPR clauses will be met before the pivotal clinical trials start.</p> <p>Proposed Changed Text</p> <p><i>Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start.</i></p>	The comment is acknowledged. See comment 742.
747	L598	14	<p>Comment: The time by which the relevant GSPRs are met seems unspecific</p> <p>Proposed change (if any): by the time the pivotal clinical trials including a device start, at the latest</p>	The comment is acknowledged. See comment 742.
748	L598	35	Clarify what kind of clinical trial is considered pivotal. Clarify if only phase 3 studies are considered pivotal or if also phase 2b studies are included.	The comment is acknowledged. It is outside the scope of this quality guideline to further define "pivotal clinical trials".
749	L601-602	19	<p>Comment: Although there may not be pharmaceutical 'GMP' legislation that specifically requires an integral device to meet the relevant GSPRs prior to use in a human clinical study, there are some further considerations:</p> <p>EC Rules governing Medicinal Products in the EU, VOL 10 – Guidance documents applying to clinical trials, Q&A v11.0 May 2013 DRAFT states:</p>	The comment is acknowledged. See comment 742. Furthermore, this is not within the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Q1.6: A study might involve a medical device – what does this mean in terms of EU regulation of clinical trials?</p> <p>Answer a) states that a Medicinal Product with an integral 'delivery product' would be managed under 2001/20/EC, referencing also B2.1 of MEDDEV 2.1/3 rev3.</p> <p>MEDDEV 2.1/3 rev3 B2.1 Identifies Drug-delivery products that are regulated as Medicinal Products, and states that "According to the MDD, this single product is governed by the MPD but the relevant essential requirements of Annex I to the MDD shall apply as far as the safety and performance-related device features are concerned.</p> <p>Answer b) states that for studies where the object is a medicinal product where during the study devices are used, the medical devices not being the object of the study have to comply with the EU-rules for the placing on the market and putting into service of medical devices.</p> <p>Answer c) discusses studies where both the device and the medicinal product are the object of the study; in which case the device is subject to the 'EU-rules applicable to medical devices'.</p> <p>It is recognised that the above relate to the current MDD; however, it is assumed that the same principles will prevail under MDR, at least until revision.</p> <p>One part of the pretext related to device constituents of a single integral Medicinal Product is that the device would be considered a Medical Device if it were to be used standalone.</p> <p>In parallel, if a non CE-marked integral device is used in a clinical study, that 'device' is effectively investigational (since</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>it does not have a market authorisation and has not had its safety and performance assessed).</p> <p>As such the Medicinal Product clinical study can also in principal be considered a clinical investigation* of a Medical Device. MDR states that Medical Devices used in a clinical investigation must 'conform to the applicable general safety and performance requirements set out in Annex I apart from the aspects covered by the clinical investigation' [MDR Article 62 General requirements regarding clinical investigations conducted to demonstrate conformity of devices; 4; (l)]</p> <p>* 'clinical investigation' is defined within MDR as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.</p> <p>Proposed change (if any): Clarify the text to reflect current guidance relating to requirements for devices used in clinical studies.</p>	
750	L607	9	<p><u>Comment</u></p> <p>Changes may require pharmaceutical performance data to be submitted as well as safety and efficacy</p> <p><u>Proposed Changed Text</u></p> <p><i>Where changes are made to the device, data to bridge the different device designs from a quality, safety and efficacy perspective may be required in Modules 3 and 5.</i></p>	The comment is acknowledged. The text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
751	L607-610	22	<p>Proposed change:</p> <p>An risk assessment should be included in Module 3.2.P.2.4, which should describe the changes to the device, the batches used and trial(s) affected, and what the mitigation or testing was performed to ensure that minimise the impact on product quality was minimal.</p> <p>Comment:</p> <p>The assessment provided in the Module may not technically be a risk assessment, so PDA recommends referring to it as only an assessment. Further, because testing may show that no mitigation of risks is necessary, we suggest that the assessment note either the mitigation or the testing performed.</p>	The comment is acknowledged. The text has been revised.
752	L610	28	<p>Comment:</p> <p>Section is a general requirement to have "Change Control" during medical device development and during pharmaceuticals development; however, reference is missing to guidance on considerations of the manufacturer</p> <p>Proposed change (if any):</p> <p>Add: It is recommended to seek guidance in ISO 20069 regarding change control.</p>	The comment is acknowledged. No change is made and reference to specific ISO standards is not considered appropriate..

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
753	L611	14	<p>Comment:</p> <p>It is more likely that device investigation cannot be separated from drug investigation in the prior example – integral DDC.</p> <p>There should be clear reference to the MDR that a CE certificate should be obtained for the device prior to the clinical studies. Additionally, in order for a co-packed device to have obtained its CE-marking authorisation, Clinical Evaluation/Investigation must have already been provided to the Notified Body. When the MAA is submitted, the CE-marking authorisation certificate needs to be provided within the MAA. It is therefore unclear what scenario is being described here.</p> <p>Proposed change (if any):</p> <p>Relocate the text to precede both Integral and Non-integral DDC paragraphs. Explain the scenario more clearly to avoid clinical study data being unnecessarily provided to Notified Bodies; and to avoid Device Clinical Investigations being specifically required from co-packed devices in drug pivotal trials.</p> <p>Confirmation is requested if the discussion of the clinical investigation should <u>only</u> be part of the pivotal study report, or if it could be addressed also in other dossier sections.</p>	The comment is acknowledged. The text has been amended.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
754	L611	19	<p>Comment:</p> <p>It is more likely that device investigation cannot be separated from drug investigation in the prior example – integral DDC. Additionally, in order for a co-packed device to have obtained its CE-marking authorisation, Clinical Evaluation/Investigation must have already been provided to the Notified Body. When the MAA is submitted, the CE-marking authorisation certificate needs to be provided within the MAA. It is therefore unclear what scenario is being described here.</p> <p>Proposed change (if any):</p> <p>Relocate the text to precede both Integral and Non-integral DDC paragraphs. Explain the scenario more clearly to avoid clinical study data being unnecessarily provided to Notified Bodies; and to avoid Device Clinical Investigations being specifically required from co-packed devices in drug pivotal trials.</p>	The comment is acknowledged. See comment 753.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
755	L611-614	8	<p>Comment:</p> <p>Clarification seems to be necessary concerning the wording: "<i>Non-integral DDC: where (device) clinical investigations were incorporated into the pivotal DDC clinical trial, because of their relevance to the MAA and because they could not be separated from the investigation of the medicinal product, the rationale for this approach should be discussed and justified in Module 5.</i>"</p> <p>This sentence is very difficult to understand. We tried to anticipate the authors intension in the below proposed changes.</p> <p>Proposed change (if any):</p> <p><u>Non-integral DDC: where when (device) clinical investigations (device) were incorporated into the pivotal DDC clinical trial, because of their (with relevance to the MAA), the following conditions should be met:</u></p> <p>1) and because they the clinical investigation of the device could not be separated from the clinical trial investigation of the medicinal product;</p> <p>2) the rationale for this approach should be discussed and justified in Module 5.</p>	The comment is acknowledged. See comment 753.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
756	L611-614	3	<p>Comment:</p> <p>The approaches for both Integral and Non-integral DDCs in this context are similar in some aspects. Differences between Integral and Non-integral DDCs are not presented clearly.</p> <p>Proposed change (if any):</p> <p>Similarities in the approaches for Integral and Non-integral DDCs could be named in one paragraph and differences highlighted clearly thereafter for better comprehensibility.</p>	The comment is acknowledged. See comment 753.
757	L611-614	20	<p>Comment:</p> <p>There may be (rare) situations where a change may be made to a non-integral DDC during pivotal clinical trials, in which case the same provisions as stated in lines 601-610 on integrated DDCs would also apply.</p> <p>Proposed change (if any):</p> <p>Make clear that any change to a non-integrated DDC during pivotal clinical trials must also be described, evaluated and justified in terms of any potential impact of the changes on the quality, safety and efficacy of the medicinal product.</p>	The comment is acknowledged. See comment 753.
758	L613-614	3	<p>Comment: Discussion and justifications for clinical approaches should be provided in Module 2 rather than Module 5.</p> <p>Proposed change (if any): Change "Module 5" to "Module 2".</p>	The comment is acknowledged. See comment 753.
<u>8. LIFECYCLE MANAGEMENT (L615-642)</u>				

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
759	L615	9	At present, the EU Variations Regulation and the associated variations guidelines do not cover a wide variety of possible changes and modifications that may affect the device constituent of a DDC during the lifecycle of the product (e.g. only addition/replacement/deletion of an integral or not integral device are considered, while the variations for container closure system are limited to some aspects or some pharmaceutical forms). Please consider the possibility to revise and update the Guideline on the details of the various categories of variations in order to widen the number and types of variations applicable to both integral and not integral device constituent of a DDC.	The comment is acknowledged. This is not within the scope or remit of this guideline.
760	L615	14	<p>Comment:</p> <p>Definition of substantial change should be added (there is no anymore mention of "Substantial" change).</p> <p>The terminology "Substantial change" was used in EMA Q & A document EMA/37991/2019, issued on 27 February 2019.</p> <p>Proposed change (if any):</p> <p>Suggestion to develop this section for substantial changes, as proposed in EMA Q & A document including the type of information expected within a Notified Body Opinion for a device change requiring a variation application, and for which no NBOP was not included initially, due to Marketing Approval prior to date of applicability of Article 117.</p>	The comment is acknowledged. It is not feasible to cover all scenarios in the guideline, and furthermore, defining the scope of a Notified Body Opinion review is outside of the remit of this guideline. There is no legal definition for term substantial which has been removed from the final guideline and updated Q&A.
761	L615-619	18	<p>Comment:</p> <p>The submission of EU Variation Regulations can only apply for integral DDCs which are regulated as a medicinal product and cannot apply for non-integral DDCs, such as co-</p>	The comment is acknowledged. The co-packaged product is considered a part of the marketing authorisation and thus subject to change by way of variation.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>packaged or cross-labelled devices, for which changes to the medical device shall be managed by the Device manufacturers QMS with NB involvement as per the requirements of the MDR 2017/745. This is further supported by the statement of line 626 that states the medicine's CA that issued the MA is to agree to the category prior to submission of the variation application</p> <p>Proposed change (if any):</p> <p>Clarify the differences between Integral and Non-Integral expectations... <i>A change listed in the variation guideline will require a variation of the appropriate category to be submitted to the medicines CA(s). For integral DDCs, all changes to the medical device designs and/or device components within DDCs should be presented in accordance with the relevant EU Variations Regulation and associated variation guidelines in place and should be submitted under the appropriate category.</i></p>	
762	L615-627	23	<p>The medical device manufacturer must notify the marketing authorisation holder of the medicinal product of all changes. The marketing authorisation holder should take due account of the change in accordance with the rules governing variations to the marketing authorisation for its medicinal product.</p> <p>This is important because medical device manufacturers are not in a position to determine which changes must be reported. It is already difficult for them to identify substantial changes requiring recertification for CE marking purposes.</p>	The comment is acknowledged. The text has been updated.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
763	L616-627	3	<p>Comment:</p> <p>It is not clear which data and/ or documentation will be assessed by the Notified Bodies or the Competent Authorities, respectively. Double filing and double assessment will lead to ambiguities and should be avoided.</p> <p>Proposed change (if any):</p> <p>Provision of more detailed information about responsibilities of the Notified Bodies and the Competent Authorities for assessment of DDC related changes during product lifecycle.</p>	The comment is acknowledged. Reference is made to the core precept regarding responsibilities of Notified Bodies and National Competent Authorities.
764	L616-619	16	<p>Comment:</p> <p>EU Variations Guideline (2013/C 223/01) Table B.IV does not provide enough guidance for the different types of devices and classification of changes or if a change in the drug part would generate a mandatory update in the device part to e.g. updated standards or regulations covering the device part or vice versa.</p> <p>Proposed change (if any):</p> <p>More guidance is needed concerning changes and the impact of changes both for device and drug parts in combination products. Propose EMA to have discussions with Medical Device Regulators for harmonised view and wording. Propose to include a flowchart of variation/change notification process of drug-device combinations. Suggest to provide a high level decision flow for the evaluation of the significance of a device change, from safety and effectiveness perspective.</p>	The comment is acknowledged. See comment 760.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
765	L617	14, 31	<p>Comment: The guideline suggests that “all” changes to a medical device or component should be presented in relevant variations. The use of all is burdensome as not all design elements for devices are included in an initial MAA content for approval.</p> <p>Proposed change (If any): Suggest deletion the word “all’ or qualifying the statement to mean changes that can significantly impact the safety, effectiveness, performance or usability of the device or DDC.</p>	The comment is acknowledged. The text has been amended.
766	L620	5	Is the EU-variation guidance going to be updated to clarify which change would require a new NBOP?	The comment is acknowledged. See comment 759.
767	L620-622	14	<p>Comment:</p> <p>Further guidance is needed regarding this point, suggest inclusion of some examples of device changes that would require updated documentation.</p> <p>For lifecycle changes, the MAH needs to consider whether any updates are needed, such as to the NBOP or other documentation associated with the device.</p> <p>The Applicant must submit certain data and documentation to a Notified Body in order that an NBOP can be formed on conformity to relevant GSPRs. It must therefore be fundamental that any change to said data may influence the Notified Body opinion. Otherwise, changes that are deemed not to fall under medicinal product variation guidelines go un-checked and positive NBOPs become effectively invalidated.</p> <p>In such a case, it seems logical that the MAA Holder should inform the NB and seek clarification of whether the change</p>	The comment is acknowledged. See comment 760

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>would affect the NB opinion. This step should be independent of the requirement to inform the competent authority under variation guidelines.</p> <p>1) If the Notified Body conclude that their opinion would change, then further data or documentation need to be submitted to the NB to 'maintain' the positive NBOp. This updated NBOp would then need to be submitted to the competent authority IF required under variation guidelines, however this may not be necessary.</p> <p>2) If the NB do not see that their opinion would change, then the process should be as described – and subject to variation guidelines an updated NBOp may still be required to support the submitted variation.</p> <p>For a co-packaged drug-device combination, it is our understanding that periodic updates of CE certificate or declaration of conformity should not require an update of the MAA file.</p> <p>In which cases would an updated CE certificate and DoC be required to be submitted?</p> <p><u>Proposed change (if any):</u></p> <p>Review the different scenarios for change and provide appropriate guidance for these.</p> <p>Clarify what is needed to support a decision that no updates to the device documentation are needed.</p> <p>This should include information previous stated in EMA Q&A document, Section 1.7.</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
768	L620-622	18	<p>Comment:</p> <p>This paragraph states that the MAH is responsible for determining if updates to relevant documentation associated with the device are required to support the change and lists as examples of such documents, the NB Opinion, Declaration of Conformity and CE-mark. Reference to CE-mark in this respect is not relevant and it is not clear if it was intended instead to state a copy of a revised CE Certificate.</p> <p>Please note that the Conformity Assessment process for medical devices does not provide a product approval, as such, and NBs are only involved in assessment of changes to the device design or intended use for high risk devices.</p> <p>Proposed change (if any):</p> <p>Remove reference to CE-mark from the examples provided or clarify the intention of inclusion of CE-mark.</p> <p><i>Depending on the nature of the change, the MAH should consider whether updates to relevant documentation (e.g. NBOp, Declaration of Conformity, CE-mark etc.) associated with the device in question are required to support the change.</i></p>	The comment is acknowledged. The text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
769	L620-622	19	<p>Comment: Further guidance is needed regarding this point.</p> <p>The Applicant must submit certain data and documentation to a Notified Body in order that an NBOp can be formed on conformity to relevant GSPRs. It must therefore be fundamental that any change to said data may influence the Notified Body opinion. Otherwise, changes that are deemed not to fall under medicinal product variation guidelines go un-checked and positive NBOps become effectively invalidated.</p> <p>In such a case, it seems logical that the MAA Holder should inform the NB and seek clarification of whether the change would affect the NB opinion. This step should be independent of the requirement to inform the competent authority under variation guidelines. If the Notified Body conclude that their opinion would change, then further data or documentation need to be submitted to the NB to 'maintain' the positive NBOp.</p> <p>This updated NBOp would then need to be submitted to the competent authority IF required under variation guidelines, however this may not be necessary.</p> <p>If the NB do not see that their opinion would change, then the process should be as described – and subject to variation guidelines an updated NBOp may still be required to support the submitted variation.</p> <p>Proposed change (if any):</p> <p>Review the different scenarios for change and provide appropriate guidance for these.</p>	The comment is acknowledged. See response to comment 760.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
770	L620-622	24	<p>Comment/ Quote</p> <p>Line 620 – 622 states: <i>"Depending of the nature of the change, the MAH should consider whether updates to relevant documentation (e.g. NBOp, Declaration of Conformity, CE mark etc.) associated with the device in question are required to support the change"</i></p> <p>Proposed change</p> <p>This statement should be harmonized with EMA’s “Q&A on implementation of the Medical Devices and In vitro Diagnostic Medical Devices regulations”. According to these Q&As any substantial change to the design or intended purpose of the device component or addition or full replacement of the device component requires the submission of new/updated NBOp, Declaration of Conformity, CE mark as part of the variation/extension application</p> <p>It should be noted that in line with the Q&A document only substantial changes are subject of notification to the NB.</p>	The comment is acknowledged. See response to comment 760.
771	L620-622 and L628-642	31	<p>Comment:</p> <p>In devices, it is expected that a Notification of Change (NoC) is submitted to the Notified Body if there is any impact to the Essential Requirements (now General Safety and Performance Requirements; GSPRs). NoCs are also submitted when there is a substantial change to the quality system that manufactures the device. It does not seem like the GSPRs or QS impact of changes is considered in this section of the EMA document.</p>	The comment is acknowledged. The proposal is outside of the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change:</p> <p>With the NB being held responsible for device conformance, we would think that they would want the same process followed for devices. It would also be helpful for consistency of expectations regarding NoCs from the manufacturers' viewpoint as well.</p>	
772	L621	22	<p>It would be helpful to include more guidance about the changes that might require updates to relevant documentation for DDCs. For instance, could a change in formulation/concentration or clinical use (new indication) of the medicinal product (but without a change to the design of the device component) trigger a request for a new NBO?</p>	<p>The comment is acknowledged. See response to comment 760.</p>
773	L622	5	<p>Comment:</p> <p>Apart from changes to the device part, the MAH should also consider that substantial changes to the drug part (e.g. increased volume, higher viscosity), may impact the performance of the device part that could require further verification and validation. In addition, changes in the intended use or target population may require an additional usability study to evaluate whether the DDC can be used safely to deliver the medicinal product to the new target population.</p> <p>Please note that variations/ changes to devices are expected to occur more often during the life cycle compared to medicinal component of the DDC.</p> <p>Does the current variation guideline sufficiently cover such variations for the MAH to appropriately categorize these into type IA/IB or Type II variations?</p>	<p>The comments are acknowledged.</p> <p>The text has been amended to include information about changes to the medicinal product affecting the device.</p> <p>Updating the variations guideline would have to be initiated by the Commission.</p> <p>Legacy products are covered in the EMA Q&A.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Another comment is how to define significance as it varies between products.</p> <p>NB's concern is that Pharma will have a tendency to downplay the significance of device changes.</p> <p>The routine GMP inspections from medicines CA may cover the change management process/system however the auditors are not 'device-competent'. Additionally, there will be no surveillance audit or equivalent by an NB in the NBOP model.</p> <p>Ultimately there will be no 'control' or check of the Manufacturer's assessment of change.</p> <p>Should the NB not have a role in agreeing with the manufacturer that the device change is / is not substantial? The Pharma company may have the view that the change is insignificant but actually the associated data/ documentation/ information may have been pivotal to the NB granting their opinion.</p> <p>Another concern is the combined effect of several 'minor' changes over time. These are not going to be detected in a Pharma company that sees the device constituent simply as 'packaging'.</p> <p>It is not clear if lifecycle management issues related to MAA/device manufacturer supplier control are checked within GMP inspections (for devices, this is normally covered by NB audits and change management).</p> <p>It is not clear how to handle the art 117 devices that were placed on the market before May 26, 2020 but never had a NBOP and now offer a change requiring NBOP. Does the NB</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>need to assess all applicable GSPR to the device or only the ones affect by the change?</p> <p>Proposed change (if any):</p> <p>Please consider including the above examples in the guideline to increase awareness that the changes to the drug part may impact the GSPR's of the device part and may require additional NBOP's. In addition, please consider updating the variation guideline to get a better alignment with device changes. In doing so, please consider the relevant examples in the NBOG document on design changes (NBOG BPG 2014-3). Taking the above concerns into account, it may be beneficial to involve the Notified Body in the decision making whether a change is substantial or not. Perhaps an annual device change report to NB's with a subsequent update of the NBOP is a model that could work.</p> <p>Please include guidance on how to handle devices that never had a NBOP before but have been placed on the market without CE mark.</p>	
774	L623-625	14	<p>Comment:</p> <p>It should be recognised that the NBOP is not based upon DDC CQAs, but upon satisfaction of the relevant GSPRs. Therefore, changes that affect DDC CQAs are not necessarily relevant to the NBOP, and vice versa.</p>	The comment is acknowledged. No change is required to the guideline text.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
775	L623-625	19	<p>Comment:</p> <p>It should be recognised that the NBOp is not based upon DDC CQAs, but upon satisfaction of the relevant GSPRs. Therefore, changes that affect DDC CQAs are not necessarily relevant to the NBOp, and vice versa, see also comments above.</p>	The comment is acknowledged. No change is required to the guideline text.
776	L623-627	19	<p>Comment:</p> <p>Industrialisation (or 'scale-up') of device manufacturing typically introduces increased variation and may require adjustment of specifications once that variability is fully understood. Scale-up may occur both in the development/clinical phases and in the lifecycle phase. It is not clear where EMA see such 'change' in the context in variation.</p> <p>Proposed change:</p> <p>Clarify EMA perspective on specification changes arising from scale-up induced variation change. Clarify requirement to inform Notified Body and/or medicines Competent Authority of such changes.</p>	The comment is acknowledged. See comment 760.
777	L625	35	In case of the need of variation is not easily categorized vs the EU variation regulation or a change category is unclear, is it required a consultation prior the submission of the variation? If yes, what is the process? Explanatory examples would be useful.	The comment is acknowledged. Regulatory advice is outside of the scope of this guideline.
778	L626	14	Comment:	The comment is acknowledged. This is not within the remit of this guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>In cases where the need for a variation and/or the category if the change is unclear, it is recommended that...</p> <p>It shall be noted that the current variations guideline does not consider DDCs and possible changes that could be filed.</p> <p><u>Proposed change (if any):</u></p> <p>Consideration for future alignment of variations guidance is needed to account for better categorisation for typical DDC changes.</p>	
779	L626	5	Will the medicines CA also consult the NB?	The comment is acknowledged. Medicines CA will not consult NBs; individual responsibilities are defined in the core precept.
780	L628-642	23	<p>Will all changes to dosing devices be subject to the requirements for type II variations?</p> <p>A detailed statement on the analysis of the risks arising from the change to the device should be included in the EPAR.</p>	<p>The comment is acknowledged. The category of variation should take into account the impact of the device change(s) on the quality, safety and efficacy of the medicinal product. Reference is also made to the updated Q&A (June 2021) on the MDR implementation.</p> <p>The content of the EPAR is outside of the remit of the guideline.</p>
781	L628-642	28	<p>Comment:</p> <p>The MDR requires a very active update of the risk management file – including risk assessment of changes to a device. If this triggers variations a catch 22 dilemma will arise, as the variations will slow all of this down to an unacceptable level.</p>	The comment is acknowledged. This is outside of the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
782	L629	6	'change or replace'. We would consider 'addition' also a likely option for a variation.	The comment is acknowledged. The text has been revised accordingly.
783	L629-631 Also applies to L637-638	14	<p>Comment:</p> <p>Expand the scope to include all aspects of user interface of the product that have changed, not just changes to the device. Additionally, replace the term "user error" with "use error" to generalize the type of errors that could occur with use to not be just those originating from user mistakes but any use-related issue including those originating from poor product design that induces use-errors.</p> <p>Proposed change:</p> <p>(lines 629-631): In cases where a variation is submitted to change or replace the device or other aspects of the user interface of a DDC, consideration should be given to whether there is an impact on the instructions for use between current and proposed devices products, and any potential risks of user use or medication error.</p> <p>(lines 637-638): If the instructions for use are different between current and proposed devices products, the potential risks of user use error and the potential for medication errors, should be considered.</p>	The comment is acknowledged. The text has been revised accordingly.
784	L631-632	8	Reference for the appropriate place in the dossier is needed for " <i>The overall risk assessment of the DDC should be updated accordingly.</i> ", because there are several risk assessments possible: the one for the device according to ISO 14791 in module 3, section 3.2.P.2 (see line 242 of this draft guideline) and the RMP in module 1, section 1.8.2.	The comment is acknowledged. To ensure flexibility, the guideline will not define locations.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
785	L634-636	24	<p>Comment</p> <p>This bullet point is not needed as it does not give new information. The timing when the applicant makes available the new version of device is given in the application form (implementation date). The currently registered version of the device will remain on the market until the end of shelf-life of the respective medicinal product, if not recalled earlier for safety reasons.</p> <p>Proposed change</p> <p>Delete section.</p>	The comment is acknowledged. The text has been revised.
786	L637-640	8	<p>For considerations on potential medication errors and human factor studies we would recommend to cross reference the specific parts of the guideline in sections 5 and 6.</p>	The comment is acknowledged. No change to the guideline is proposed.
787	L639-640	14	<p>Comment:</p> <p>The text refers to "Human factors/usability studies" but this is confusing and not consistent with IEC 62366-1:2015. Risk-based assessments should be made for whether human factors validation (summative) studies need to be done, as sometimes summative testing may not be required based on an acceptable product use risk profile.</p> <p>Proposed change (if any):</p> <p>Usability studies may be required, as determined by a use-related risk assessment.</p>	The comment is acknowledged. The text has been revised accordingly.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
788	L641-642	14	<p>Comment:</p> <p>Clarify if RMP refers to the Device Risk Management Plan or the Clinical Risk Management Plan. Medication errors related to the use of the device for non-integrated CE-marked device are normally documented in the device risk management, part of CE-marking. This is governed by the Medical Device Directive for CE marked devices. Safety signals from the field are captured through the PMS and not the PV system, thus not through RMP.</p> <p>Proposed change:</p> <p>Propose to add: “For non-integrated CE marked devices, potential risks of medication errors or misuse should be documented. The MAH should reference the link between the Post Marketing Surveillance and Pharmacovigilance.”</p>	The comment is acknowledged. Detailed aspects of post-marketing surveillance and pharmacovigilance are outside the scope of this quality guideline. No change to the test is proposed.
789	L641-642	6	Risks related to medication errors should primarily be addressed by appropriate labelling/IFU.	The comment is acknowledged. It is not considered necessary to add further text.
790	L641-642	10	This is the only mention of the RMP – will there be other expectations or clarity provided on what is needed within the RMP for DDC	The comment is acknowledged. See comment 788.
<u>9. EMERGING TECHNOLOGIES (L643-652)</u>				
791	L643-652	27	EFA welcomes EMA’s acknowledgement that the advancement of science and technology for medical devices does not go hand in hand with the one for medicinal products . This imbalance is an issue that lies at the heart of DDCs, as the compatibility between devices and	The comment is acknowledged. The comment is out of scope of the guideline; however, clarification has been made.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>drug products constitutes a vital factor for the DDCs efficacy and safety aspects. Especially in our disease areas, EFA patients witness extensive developments in the field of devices, exemplified by smart inhalers, air purifiers etc, without necessarily taking fully into account the progress in medicinal products.</p> <p>Although the advancement of technology and innovation is mostly beneficial, EFA thinks that the resulting asymmetry in the case of DDCs creates more immediate uncertainties for patients than solutions. A contributing factor in this respect is the lack of adequate training of patients into new and innovative device technologies, which would be vital, especially for patients with chronic conditions.</p> <p>We would therefore like to urge EMA to focus its efforts on preserving a healthy balance by promoting policies that help in bridging, rather than widening, the gap between the two. Moreover, we feel that EMA should propose a framework introducing patients into new and innovative devices, providing training in lay language in both physical and electronic forms, and ensuring the smooth transition from one device technology to the other. In particular, proposals should promote the simplification of administration of drugs (e.g. in the case of triple therapy), the use of less technical information and much clearer and more understandable text. Providing less technical information and much clearer and more understandable text would meet patients' needs and ensure safer administration of drugs.</p>	
792	L644 – 652	14	Clarification is requested regarding interaction with NB	The comment is acknowledged. Reference is made to the core precept regarding responsibilities.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
793	L646-647	20	ACRO welcomes the recognition that flexibility is needed for emerging technologies.	The comment is acknowledged.
794	L649	8	Please specify which Innovation Office(s) may be addressed, the EMA Innovation Office or those established by the national competent authorities?	The comment is acknowledged. The route taken is decided by the applicant.
795	L649	23	Discussions between EMA and marketing authorisation applicants or holders to obtain scientific advice can generate conflicts of interest. The fact that the detailed minutes of these discussions are not made public fuels doubts over EMA's independence from the health products industry.	The comment is outside of the scope of the guideline and is not agreed. Reference is made to EMA website for further information: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance https://www.ema.europa.eu/en/about-us/how-we-work/handling-competing-interests
796	L651	14	<u>Comment:</u> Is the expectation only for emergent devices that samples be provided? Include option for a MAH to demonstrate use of a product rather than shipping samples to the assessor(s) <u>Proposed change (if any):</u> Clarification that more established devices, i.e. PFS, PFP or inhalers are not required	The comment is acknowledged. Text in Section 4 has been revised.
797	L652	6	<u>Comment:</u> The NfG currently states that it is encouraged to provide samples to NCAs, but this could be worded more strongly,	The comment is acknowledged. Refer to comment 796

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			i.e. 'required' as this really helps in the assessment of such DDCs.	
<u>10. DEFINITIONS (L653-704)</u>				
798	L653	14	<u>Proposed change</u> (if any): Add definition for ATMP	The comment is acknowledged. The ATMP definition is added.
799	L653	14	<u>Comment:</u> Lines 56-58 recognize that the user is sometimes the patient self-administering and sometimes a lay or professional caregiver, but it is unclear later in the document who the user might be. <u>Proposed change (if any):</u> Add definition of "user", ideally the one in IEC 62366-1 (subclause 3.24): "person interacting with (i.e. operating or handling) the medical device"; it might be good to include a note saying that the user could be the patient self-administering or a lay or professional caregiver administering the injection to the patient.	The comment is acknowledged. It is not in the scope of this guideline to define user from a medical device perspective.
800	L653	22	<u>Comment:</u> PDA suggests that EMA include the following definitions modified from the IMDRF Common Data Elements for Medical Device Identification (IMDRF/RPS WG/N19), as more clarity around the term "reusable" is highly desirable. <u>Proposed additional text:</u>	The comment is acknowledged. The differentiation between single use and single patient use devices is specific for medical devices and not in the scope of the guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Single Use Device: A medical device intended by the manufacturer to be used on an individual patient during a single procedure.</p> <p>Reusable - Single Patient Use Device: A medical device intended by the manufacturer to be used on a single patient, that can be refilled with additional medicinal product.</p> <p>Reusable - Multi-Patient Use Device: A medical device intended by the manufacturer to be used on multiple patients with reprocessing (e.g. cleaning disinfection or sterilization) between uses.</p>	
801	L653	28	<p>Comment:</p> <p>Missing definitions:</p> <ul style="list-style-type: none"> • Container vs. medical device component (Clarification needed) • Constituent part of a MA (line 689) • Quality Aspect (line 136) 	<p>The comment is acknowledged.</p> <p>The CCS definition is now consistent with the EMA packaging guideline, with an additional clarification regarding medical devices (parts).</p> <p>“Quality aspect” is a general term to be understood in the context mentioned in the guideline, and therefore is not included in the definitions.</p>
802	L656	14	<p>Proposed change (if any): Control Strategy (as per ICHQ10)</p>	<p>The comment is acknowledged. The proposed change is accepted.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
803	L658-661	14	<p>Comment:</p> <p>This should be updated to be more consistent with the intent of the document. The current definition focuses on the drug substance and drug product. It should be expanded to include the device component of the drug-device combination.</p> <p>Proposed change (if any):</p> <p>...The controls can include parameters and attributes related to drug substance and, drug product, and device materials and components, ...</p>	The comment is acknowledged. The proposed rewording is modified.
804	L662-664	3	<p>Comment:</p> <p>It is not clear what is meant by Container Closure System. This term has been used for materials/components with direct contact to the medicinal product. Are integral devices (e.g. autoinjectors, pens, needle guards) which do neither have direct contact to the medicinal product nor provide protection of the medicinal product considered to be a Container Closure System?</p>	The comment is acknowledged. See comment 801.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
805	L663	28	<p><u>Comment:</u></p> <p>Should be rephrased to make clear that the CCS only includes the aspect of the device that serves to contain and protect the device.</p> <p><u>Proposed change (if any):</u></p> <p>Proposed definition of Container Closure System (CCS): The sum of components, including devices, that together contain and/or protect the medicinal product as defined in Section 1 of this guidance.</p>	The comment is acknowledged. See comment 801.
806	L670	14	<p><u>Comment:</u></p> <p>Definition of DDC describes it as a medicinal product that is necessary for the administration, correct dosing or use of the medicinal product.</p> <p>If the DDC is the medicinal product, then it cannot be used to administer the 'medicinal product' i.e. this is a circular definition.</p> <p><u>Proposed change (if any):</u></p> <p>Revise definition of DDC to be:</p> <p>A medicinal product(s) with integral and/or non-integral medical device/device component(s) necessary for the administration, correct dosing or use of the medicine.</p>	The comment is acknowledged. There is no legal definition for the term DDC and it has been decided to remove it from the final guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
807	L674-676	18	<p>The definition of the Drug Product Manufacturer is not explicitly clear in this sentence. Is the intention that this defines the physical location and commercial entity who are responsible for the manufacture /co-packaging of the final DDC product?</p> <p>For a non-integral DDC, the device could be physically manufactured by an entity who does not take on the legal obligations as the device manufacturer, so it is not clear how far down the supply chain this definition shall apply.</p>	The comment is acknowledged. The definition of medicinal product manufacturer has been revised.
808	L675-676	28	<p>Comment:</p> <p>The definition is not crisp and clear – non-integral DDC is now used differently than previously</p>	The comment is acknowledged. See comment 807.
809	L676	14	<p>Comment:</p> <p>Reference should be made to drug product instead of DDC</p> <p>Proposed change (if any):</p> <p><i>"DDC drug product"</i></p>	The comment is acknowledged. See comment 807.
810	L677	28	<p>Comment:</p> <p>Medical Device Manufacturer, current definition is misleading. There is no need to bring life-cycle in play. "Incorporation" in this context is misleading. Manufacturer may assemble drug part with device part. Term incorporation might not take the full spectrum of combination into consideration". See also comment to line 83 – definition of combination.</p>	The comment is acknowledged. The text has been revised.
811	L677-679	14	<p>Comment:</p>	The comment is acknowledged. The definition of Device Manufacturer cannot be aligned because the medical device will not be

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The definition of Device Manufacturer should be more aligned to the EU-MDR definition of Manufacturer (Art. 2(30)).	marketed under the name of the device manufacturer.
812	L677-679	18	<p><u>Comment:</u></p> <p>The definition of Device Manufacturer and the intended scope is not clear. As stated in the definition, it covers the commercial entity manufacturing and supplying devices or components, that does not imply that this entity would generate the Declaration of Conformity or hold the CE Certificate for the device. For a non-integral DDC, the device could be physically manufactured by an entity who does not take on the legal obligations as the device manufacturer, so it is not clear how far down the supply chain this definition applies and if it extends beyond the legal device manufacturer</p>	The comment is acknowledged. See comment 811.
813	L677-679	24	<p><u>Comment</u></p> <p>This definition varies from the MDR and could lead to confusion (OEM, pure producers of medical devices, are not meant but manufacturers in the legal sense).</p> <p><u>Proposed change</u></p> <p>Use MDR definition: Device “manufacturer’ means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark”. The device manufacturer corresponds to the market authorization holder of medicinal products.</p>	The comment is acknowledged. See comment 811.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
814	L683	14	<p>Comment:</p> <p>Not all marketing authorisations are granted by the competent authorities of the Member States.</p> <p>Reference should be made to the centralised procedure under Regulation (EC) No 726/2004. Moreover, the type of product should be specified (DDC instead of "product").</p> <p>Proposed change:</p> <p>line 683: "<i>amended</i>) or the European Commission in accordance with Regulation (EC) No 726/2004 and is responsible for marketing the medicinal product (e.g. a DDC)".</p>	The comment is acknowledged. The text has been revised.
815	L685-686	14	<p>Comment:</p> <p>Need to clearly stipulate that it refers to the EU market.</p> <p>Proposed change:</p> <p>"A device that fulfils the definition of Article 2(1) MDR and is intended to be placed on the EU market, made available on the EU market or put into service in the EU."</p>	The comment is acknowledged. The text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
816	L687	14	<p>Comment:</p> <p>The term "medical device component" to be used synonymous with the "medical device" as defined under article 2(1) of the MDR deems inappropriate as industry considers medical device components only as a part of a finished medical device product. Using this new definition would be confusing and might lead to misinterpretations. To harmonize as much as possible on terminology already largely used in DDC industry, it is proposed to introduce the term "device constituent, device constituent part" as synonym to medical device component.</p> <p>Proposed change (if any):</p> <p>Add after Medical device component (synonym: device constituent, device constituent part)</p>	The comment is acknowledged. The text has been revised.
817	L688-689	14	<p>Comment:</p> <p>This definition is not easy to read. "... marketing authorization ... "should be replaced by"...drug-device combination ..."or"... DDC..."</p> <p>Proposed change (if any):</p> <p>A device that fulfils the definition of Article 2(1) MDR, where it and that is considered a constituent part of a marketing authorization drug-device combination (integral or non-integral). It is synonymous with medical device.</p>	The comment is acknowledged. The text has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
818	L689	28	<p><u>Comment:</u></p> <p>The proposed definition is not clear - it defines a Medical Device component, and then later says it is the same as a medical device in general. Since medical devices in general are much broader than those included in a drug registration, this needs to be more specific. Also, formally, the device is not a constituent part of a marketing authorization, but of the product solution covered by that marketing authorization.</p> <p><u>Proposed change (if any):</u></p> <p>A medical device, according to the definition of Article 2(1) of Regulation 2017/745 (MDR), which is described in the marketing authorisation application as required for the use of the medicinal product.</p>	The comment is acknowledged. See comment 816.
819	L697-698	14	<p><u>Comment:</u></p> <p>Strongly recommend to use the definition of the MDR regarding device performance</p> <p><u>Proposed change (if any):</u></p> <p>Performance: The ability of the medical device to achieve its intended purpose as stated by the manufacturer.</p>	The comment is acknowledged. The text has been revised.
820	L699	14	<p><u>Comment:</u></p> <p>This does not seem to include a platform technology that is being offered by a third party.</p> <p><u>Proposed change (if any):</u></p>	The comment is acknowledged. The text has been revised, taking into account changes in Section 4.3.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Add description of platform technology (such as a pre-filled syringe)	
821	L699	11	Proposed change: Add example of platform technology (such as a pre-filled syringe) for more clarity regarding the scope of leverageable platform data.	The comment is acknowledged. See comment 820.
822	L700	10	Comment: Shape definition of platform technology Proposed change: A device configuration technology that has been approved for another medicinal product and has therefore been characterised previously.	The comment is acknowledged. See comment 820.
823	L702	14	Comment: The definition of "usability" is not consistent with the definition provided in IEC 62366-1:2015 (EU harmonized standard for medical devices). "Usability" is not also known as human factors engineering or usability engineering. Usability engineering is per standard not used as synonym for usability, but is defined as follows: USABILITY ENGINEERING: application of knowledge about human behaviour, abilities, limitations, and other characteristics related to the design of tools, devices, systems, tasks, jobs, and environments to achieve adequate USABILITY. In addition, the phrase "usability and/or human factors studies" is used in multiple places in the document and not consistent with IEC 62366-1:2015.	The comment is acknowledged. Usability refers to DDCs and not for stand-alone medical devices. The definition has been revised.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p><u>Proposed change (if any):</u></p> <p>Replace the definition of "usability" with the one in IEC 62366-1:2015 (subclause 3.6): "characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency, ease of user, learning and user satisfaction in the intended use environment". Add a definition or "usability test" (or study), ideally the one in IEC 62366-1:2015 (subclause 3.19): "method for exploring or evaluating a user interface with intended users within a specified intended use environment"</p>	
824	L702-704	9	<p><u>Comment - CRITICAL</u></p> <p>Usability and Usability Engineering/Human Factors Engineering should be defined according to IEC 62366.</p> <p><u>Proposed Changes</u></p> <p>Replace the definition of 'usability' with that from IEC 62366: "<i>Characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency and user satisfaction in the intended use environment</i>"</p> <p>Add the IEC 62366 definition for 'usability engineering or human factors engineering': <i>Usability Engineering (or Human Factors Engineering): Application of knowledge about human behaviour, abilities, limitations, and other characteristics to the design of medical devices (including software), systems and tasks to achieve adequate usability.</i>"</p>	The comment is acknowledged. See comment 823.
825	L702-704	28	<p>Comment: This definition of Usability is unfortunate. There is much more than usability involved in being able to safely deliver the medicinal product to the target population.</p>	The comment is acknowledged. See comment 823.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change (if any):</p> <p>Delete the definition.</p>	
<u>ABBREVIATIONS (L705-732)</u>				
<u>ANNEX 1: PROPOSAL FOR NOTIFIED BODY OPINION TEMPLATE (L733-807)</u>				
826	L733	14	<p>Comment:</p> <p>The NB template shall contain a date, a version and an expiry date</p> <p>Proposed change (if any):</p> <p>Add</p>	The comment is acknowledged. A Notified Body Opinion template proposal was included in the draft guideline to stimulate discussions with Notified Bodies regarding expected information in the context of a marketing authorisation, line extension or variation application. However, such template is not within EMA/CHMP remit and it was decided to remove this proposal from the final guideline.
827	L733	14	Under which legal basis are Notified Bodies expected to use this template? Notified Bodies operate under Regulation 2017/745 only	The comment is acknowledged. See comment 826.
828	L733	19	Suggested to add an annex with the list of NBs, available on Nando System, with the expertise related this type of DDCs.	The comment is acknowledged. See comment 826.
829	L733-807	3	<p>Would the EMA be able to clarify whether this template has been discussed with any NB to ensure their acceptance? and/or whether there will be an intention to share with the NBs.</p> <p>Proposed change (if any):</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Acceptability of this template from the NB perspective would need to be clarified.	
830	L733-762	10	<p>Comment: Annex 1: Proposal for Notified Body Opinion template</p> <p>Proposed Change: add</p> <ul style="list-style-type: none"> - Name of Marketing Authorization Applicant - Address of Marketing Authorization Applicant - Reference of the Technical Report associated (in the template only "administrative reference number of the NBOp" - Medical Device Category - First Issuance of the opinion - Current Issuance of the opinion <p>Section I "Summary of Notified Body Opinion" may look redundant with Section III.e "Notified Body Opinion".</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
831	L752	5	<p>Comment:</p> <p>“Reviewer name and position”</p> <p>Why is the position of the reviewer needed?</p> <p>If this statement refers to the qualification of the reviewer, position is the wrong term used: a position does not explicitly indicate anything about the person’s qualification.</p> <p>If EMA considers specific qualifications as needed, this is to be stated.</p> <p>Otherwise, each Notified Body is going to focus on its individual employee authorization scheme.</p> <p>Proposed change (if any):</p> <p>Change to “Reviewer name” only.</p> <p>Delete line, as NB authorization is still required (compare to certificate)</p>	The comment is acknowledged. See comment 826.
832	L758 and L760	14	<p>Comment:</p> <p>NB authorisation – what is the NB authorising? Is an authorisation still required if the opinion would be “not acceptable”? (Line 765)</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
833	L760	5	<p>Comment:</p> <p>“Authorisation date” What is meant by this term?</p> <p>The authorisation date of the reviewer? The authorisation date of the Notified Body?</p> <p>Proposed change (if any):</p> <p>Clarify term ´s meaning</p>	The comment is acknowledged. See comment 826.
834	L765	14, 19	<p>Comment:</p> <p>It is not the role of the Notified Body to conclude acceptability. This is the role of the competent authority. It is proposed to use ‘conforms’ or ‘does not conform’ to align with the MDR text.</p>	The comment is acknowledged. See comment 826.
835	L765	19	<p>Comment:</p> <p>It is my understanding from various recent Notified Body discussions regarding NBOps that they would be unlikely to give a single overall positive statement of conformity to the overall set of relevant GSPRs. Almost all NBOps are likely to conclude that the relevant GSPRs are NOT met by the Manufacturer’s Technical File submission.</p> <p>This is on the basis that certain relevant GSPRs will be ‘over-ruled’ by parallel Pharmaceutical legislation and therefore information will not be provided by the Applicant (in preference for providing such information for competent authority review), and cannot therefore be concluded by the Notified Body to be satisfied. These requirements are likely to be considered ‘relevant’ to the device constituent by the Notified Body; however, are likely to be considered ‘not applicable’ by the Manufacturer due to Pharmaceutical</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>legislation taking precedence. The Notified Body can only conclude that the relevant requirement is not met in their opinion. It is for the Competent Authority to accept this basis and perform review of the aspect against Pharma requirements.</p> <p>Similarly, certain GSPRs may only be partly-fulfilled by the Applicant on the same basis, and the NB can therefore not conclude conformance to the full GSPR as written.</p> <p>The Notified Body is obliged to conclude non-conformance if a GSPR is considered relevant but there is inadequate information provided.</p> <p>It is important that the competent authority can quickly ascertain the level of additional review needed on their part. Therefore, a more 'single-page' type summary could be of use.</p> <p><u>Proposed change (if any):</u></p> <p>Remove the expectation for a single high-level conformance statement. Elaborate 792-793 to provide the summary table of the GSPRs, clearly identifying relevance and the NB Opinion for each – ideally using simply 'Conforms' or 'Does Not Conform'. For those that do not conform, the NB should be requested to state the reason for this (which could also be based upon the Applicant's justification). Example standard text could be suggested e.g. 'Information not provided – requires competent authority review', 'To be reviewed under pharmaceutical legislation', 'Information not complete – requires further competent authority review' etc.</p>	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
836	L767	5	<p>It is stated that the brief summary states “any relevant constraints”. In line 765 it is said that the opinion has to be clear, i.e. a decision on acceptable or not acceptable.</p> <p>There is nothing stated on “acceptable with constraints” – this is a third category and this category does not lead to clarity.</p> <p>If it is accepted to have constraints, there is need of a guidance on constraints (e.g. a constraint catalogue) and also the consequences of such constraints are to be considered.</p> <p>This is so far not addressed on the guidance document.</p> <p>Proposed change (if any):</p> <p>EMA has to define which kind of Notified Body opinion results are possible and what are the criteria as well as consequences of such statements.</p>	The comment is acknowledged. See comment 826.
837	L776-785	18	<p>Comment:</p> <p>The suggested wording is complicated and does not add any extra value to the content of the report.</p> <p>Proposed change (if any):</p> <p>Suggest that the Basis of Assessment is limited to Article 117 of Regulation EU 2017/745</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
838	L792-793	18	<p>The scope of the assessment with a suggestion to list all applicable GSPRs and justify, as well as omissions, is potentially repetitive as there are 23 GSPRs with many sub headers and sub parts potentially also applicable or not. The NB shall within the body of their assessment detail this type of information and certainly should provide a positive / negative opinion on the manufacturers statement of GSPR applicability.</p> <p>It is not clear by the inclusion of this level of detail if the CA feels they would have a potential benefit in having this information and what action they could take should they disagree with the information provided.</p>	The comment is acknowledged. See comment 826.
839	L795	5	<p>Comment:</p> <p>Section d. Assessment (lines 796-800): <For each applicable GSPR, summarise the data presented, and final outcome(s) of the assessment>. As compliance to a GSPR is transverse and questions many assessment areas and standard (i.e GSPR 1: clinical evaluation report, risk management file, usability) this way of assessment (by GSPR and not by topics like clinical, risk management, information to users with regard to the relevant standard...) is not in line with the current way of technical documentation assessment for NBs. We consider that this approach for assessing the conformity is time consuming, not relevant and efficient and does not allow to highlight the gaps and to provide transparency in the evaluation steps.</p> <p>Currently, NB assessment reports are generally not organized per GSPR but more likely organized in the following or similar structure:</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<ol style="list-style-type: none"> 1. General Aspects 2. Device Description 3. Risk Management 4. GSPR's and Evidence of Conformity. This includes a list of international standards which is actually used by the manufacturer. The GSPR checklist identifies how each GSPR is addressed and refers to actual compliance documentation. If a GSPR is not considered applicable, the manufacturer includes a justification why it is not applicable. These lists are reviewed on completeness. 5. Summary of Design Verification/Validation. This would include compatibility with the drug (GSPR 10.3) 6. Usability. This would include compatibility with the drug (GSPR 10.3) 7. Software 8. Sterilization 9. Packaging and Shelf life. This would include compatibility with the drug (GSPR 10.3) 10. Biocompatibility. This would include leachables and extractables of the device part. 11. Animal Tissue (if applicable) 12. Clinical Evaluation (with a focus on the clinical performance and safety of the device part) 	

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>13. Manufacturing Information</p> <p>14. Instructions specifically related to the device part</p> <p>15. Conclusion of the Report (advise).</p> <p>Each identified chapter would include:</p> <ul style="list-style-type: none"> • List of Submitted manufacturer's compliance documents, including version numbers • A list of the Regulation, standards and guidance to which the Notified Body verifies compliance • Review description and results • List of questions / non-conformities which the industry should address before positive advice can be given. • At the end of the report a recommendation will be included. <p>All relevant GSPRS will be covered in the above mentioned chapters. Please advise whether this proposal may be acceptable to the EMA/CA rather than a summary for each GSPR. Please advise whether EMA requires only a summary report or a detailed report from the NB.</p> <p>A further proposal for a template of the NBOp is provided to EMA separately as annex to this document</p>	
840	L795-798	14	<p>Comment:</p> <p>It is strongly recommended to provide more detailed information in this guidance, which information should be included in the NB assessment report for EMA to feel</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			comfortable to rely on the NB assessment, in particular the assessment of the safety and performance of the device which could impact safety, efficacy and performance of the medicine. This would strongly support EMAs goal to avoid duplication of assessments.	
841	L797-798	28	<p><u>Comment:</u></p> <p>The details required in the summary report will be very challenging for the Notified Bodies. It is recommended to reduce the Notified Body Opinion report to contain concluding statements only and in turn include clear definition of Notified Body's and Competent Authority's responsibility in the assessment of the different aspects of an integral DDC.</p> <p><u>Proposed change (if any):</u></p> <p>Delete sections not related concluding statements.</p>	The comment is acknowledged. See comment 826.
842	L799	5	<p>Any changes made to the device during pivotal clinical trials should be described (changes, timelines) and the impact on relevant GSPRs discussed.</p> <p>To be deleted. Evaluation is performed against the technical documentation, not against device history files.</p>	The comment is acknowledged. See comment 826.
843	L799-800	14, 31	<p><u>Comment:</u></p> <p>Why does NB need to specifically evaluate changes during the pivotal clinical trials?</p> <p><u>Proposed change (if any):</u></p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Suggest removing the specific requirement to assess changes during pivotal clinical studies as there is no requirement for an NBOp before initiation of clinical trials.	
844	L799-800	28	<p>Comment:</p> <p>This requirement is unnecessary as the Notified Body assessment will first be conducted for the MAA which is taking place after any pivotal clinical trial.</p> <p>Proposed change (if any):</p> <p>Change to: 'Any changes made to the device after pivotal clinical trials should be described and the impact on relevant GSPRs discussed'</p>	The comment is acknowledged. See comment 826.
845	L802-804	14	<p>Comment:</p> <p>Seems unnecessary in the context of 765-767 and 793.</p> <p>Proposed change (if any):</p> <p>Remove.</p>	The comment is acknowledged. See comment 826.
846	L802-804	19	<p>Comment:</p> <p>Seems unnecessary in the context of 765-767 and 793.</p> <p>Proposed change (if any):</p> <p>Remove.</p>	The comment is acknowledged. See comment 826.
847	L807	5	What is the understanding for the term "relevant" standards, why are ISO standards specifically mentioned? Compared to harmonized standards in the form of EN ISO, EN ISO/IEC and/or e.g. AAMI.	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
<u>ANNEX 2: TEMPLATE COVER SHEET FOR NOTIFIED BODY OPINION (L808-820)</u>				
848	L808	5	<p>It should be stated in the guideline that the NBOp should be provided in full in the MAA</p> <p>Also is there any discussion between CA and NB during review of the MAA?</p>	The comment is acknowledged. See comment 826.
849	L808	14	<p><u>Comment:</u></p> <p>Annex 2: Template cover sheet for Notified Body Opinion. Consider if any link to EUDAMED information for stand-alone co-packed devices should be added.</p>	The comment is acknowledged. See comment 826.
850	L808-820	14	<p><u>Comment:</u></p> <p>The intention of the template is not clear. Under which legal basis are Notified Bodies expected to use this template? Notified Bodies operate under Regulation 2017/745 only.</p> <p>The term "stand-alone medicinal product" is not defined and could be miss-interpreted (see suggestion in the proposal). It is not clear if the technology owner (referred to in the introduction) is the same as the platform technology holder (referred to in the template), terms should be harmonized.</p> <p>In the last bullet point of the template the NB can be informed on an "Authorisation to use NBOp" which is signed by the MAH, applicant or the platform technology holder. It is assumed that a reference to an existing NBOp for a similar device (platform technology or similar individual device) is meant (see definition line 699). The template does not differentiate on content of platform devices versus non-platform devices.</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>It is not clear if the platform technology holder can apply for a NBOP on the technology without referring to a specific drug.</p> <p>It is unclear on which grounds authorization can be given by the MAH, MAA, or technology platform holder unless he is the "owner/applicant" of the NBOP in question.</p> <p>The content of the "letter of authorization" is not clear.</p> <p><u>Proposed change (if any):</u></p> <p>It is intended that this document is completed to provide information on the medicinal product with which the medical device is planned to be used. in two situations:</p> <ol style="list-style-type: none"> 1. Where an application is made for a DDC containing an individual device constituent part stand-alone medicinal product. In this case, the applicant or MAH completes this section. 2. Where an application is made that utilises a platform technology. In this case, it is the applicant or MAH fills the drug related part and references to the attached "Authorisation to use the relevant NBOP". The owner of the NBOP who completes this section, effectively providing ing a letter of authorisation to the MAH to use the data, similar to the approach used where a CEP holder authorises the use of the active substance in an EU procedure. 	
851	L810	14	<p><u>Comment:</u></p> <p>Can there be an example given of a stand-alone medicinal product?</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
852	L810-811	5	<p>It is stated that the MAH completes the cover sheet of the Notified Body opinion.</p> <p>This means that the Notified Body has no more control/oversight of the NBOp. It is understood that the cover is part of the NBOp, i.e. the whole documentation package is to be under control of the Notified Body.</p> <p>Proposed change (if any):</p> <p>The MAH may provide the data, but the whole package of the Notified Body opinion should be delivered by the Notified Body, i.e. cover sheet as well as report.</p>	The comment is acknowledged. See comment 826.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
853	L812	9	<p>Comment</p> <p>NBOP FOR PLATFORM TECHNOLOGIES: The draft guideline mentions in Annex 2 a review process and NBOP for platform technologies referring to the CEP process. This process and the role of the platform technologies owners (e.g., pharma company or device manufacturer, as the case may be) are very unclear and guidance needs to be provided. For example, it is not clear whether the technology platform holder's data are, under this process, still required to be included in CTD section 3.2.R., as this would prevent preserving confidentiality of the data. It is not clear as well whether this process authorizes the technology platform holder to take responsibility for obtaining of the NBOP for its platform technology device-constituent.</p> <p>Proposed Change:</p> <p>Consider adding a separate cover sheet template for NBOP in the case of platform technologies without details of the MAH, marketing authorisation type, procedure number and items related specifically to combination product. At the time the holder of the platform technology requests a NBOP for the platform technology, the information related to the submission details of the combination product may not be available.</p>	<p>The comment is acknowledged. See comment 826.</p> <p>Reference is also made to the updated section 4.3. and the decision to remove the reference to platform technologies.</p> <p>NBOP for platform technologies is a matter outside EMA remit.</p>

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
854	L812 and L420	14	<p>Comment:</p> <p>Please clarify how this will work as the technology owner does not hold a MAA file to bridge to? Can a technology holder obtain a NBOp without it being for a drug-device combination?</p> <p>If yes, could it then also be the Notified Body Opinion issued to the technology holder will not cover the new use as intended by the DDC MAH, and if so, would a new Notified Body Opinion then be required? What would then be assessed, and who would perform the assessment (the NB who issued the initial Notified Body Opinion or could the MAH get a new Notified Body Opinion from another Notified Body) Further clarification within the Guidance would be helpful i.e. in section "Notified Body Opinion" (420).</p> <p>Proposed change (if any):</p> <p>Clarify if this template is an appropriate authorisation for use of a platform technology</p>	The comment is acknowledged. See comment 853.
855	L812-814	31	<p>Comment:</p> <p>It is stated that this cover sheet template is to be used when an application utilises a platform technology. Many pharmaceutical companies may purchase the same model of syringe from a particular supplier for pre-filling with their medicinal product. These syringes are not typically CE marked. Providing a method to reference syringe data via a NBOp from a platform technology holder will create a less burdensome approach for marketing authorisation applicants.</p>	The comment is acknowledged. See comment 853.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Proposed change:</p> <p>Clarify if this template is an appropriate authorisation for use of a platform syringe technology</p>	
856	L812-814	31	<p>Comment:</p> <p>Please clarify if the Drug Product Manufacturer is considered as Distributor, as per MDR Article 14, for Co-Packaged non integral DDC.</p> <p>Proposed answer:</p> <p>If Article 14 of MDR is applicable, then we would request that the check of UDI be performed at the DDC assembly site only, and not along the supply chain (Wholesalers, hospital, ...), since it would not be feasible (UDI on primary packaging), or would require UDI on each packaging (First, second, third...)</p>	The comment is acknowledged. The suggested change is outside of the scope of this guideline.
857	L812-814	31	<p>Comment:</p> <p>Please clarify if a non-integral DDC assembler (Drug Product Manufacturer) of an imported device be considered as an importer, or as a manufacturer?</p> <p>Recommendation:</p> <ul style="list-style-type: none"> -Importer: Yes -Manufacturer: Only if Art 16 applicable 	The comment is acknowledged. See comment 856.
858	L812-814	31	<p>Comment:</p>	The comment is acknowledged. See comment 856.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>Please clarify if a Drug Product Manufacturer becomes a manufacturer as per MDR Art 16 while co-packaging of non-integral DDC requires to re-pack the CE marked device</p> <p>Proposed answer:</p> <p>Yes, the assumption is non-change of intended use.</p> <p>Article 16 (2b), 16 (3) and 16 (4) should be applied as long as an individual sales unit is separated into individual units (typically this is seen with single-use syringes).</p> <p>An agreement with the device manufacturer would prevent the application of article 16 as the supplier would meet Drug Product Manufacturer needs.</p>	
859	L812-814	31	<p>Comment:</p> <p>CE marking for Co-packaged device: Who does decide on the minimum validity of a certificate?</p> <p>Proposed answer:</p> <p>Use an interpretative guideline using a risk-based approach to promote harmonization as much as possible between Notified Bodies</p>	The comment is acknowledged. It is outside the scope of this guideline but reference is made to EMA Q&A on the MDR implementation.
860	L812-814	31	<p>Comment:</p> <p>Please clarify if the Drug Product Manufacturer also has to perform annual post-market surveillance for CE-marked device component.</p> <p>Proposed answer:</p> <p>No, Drug Product Manufacturer would need to report to the Device Manufacturer and other economic operators'</p>	The comment is acknowledged. It is outside the scope of this guideline.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			<p>complaints pertinent to the use of the device, as per obligations of the Pharma Quality System (PQS), similar to Distributor role under MDR Article 14 (5).</p> <p>The Device manufacturer will do the post- market surveillance. This role and responsibilities should be in the quality agreement</p>	
861	L812-815	5	<p>It is stated that the technology owner has to complete the cover sheet of the Notified Body opinion in case of platform technologies.</p> <p>This means that the Notified Body has no more control/oversight of the NBOp. It is understood that the cover is part of the NBOp, i.e. the whole documentation package is to be under control of the Notified Body.</p> <p>The Notified Body opinion focuses on Annex I and its fulfilment which is to be shown by documented objective evidence – the Notified Body opinion is not outlined to focus on authorisation/cooperation etc. of the applicant.</p> <p>If EMA is interested in getting to know such information, this is to be handled elsewhere, but not in the cover sheet of the NBOp.</p> <p>Proposed change (if any):</p> <p>The technology owner may provide the data, but the whole package of the Notified Body opinion should be delivered by the Notified Body, i.e. cover sheet as well as report.</p>	The comment is acknowledged. Se comment 853.

Comment number	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
862	L812-815	28	<p>Comment:</p> <p>Unclear. The technology platform holder cannot authorize the MAH to use the NBOP without being 100% sure on how the drug, its use, its labeling, etc. affects the NBOP already issued – the responsibility split is unclear.</p> <p>Proposed change (if any): Change to:</p> <p>'For each applicable GSPR, summarise the final outcome(s) of the assessment'</p>	The comment is acknowledged. See comment 853.
863	L819	19	<p>There is already industry confusion regarding the applicability of the proposed template, given that the scope of the guideline is broad and covers various product types and configurations. It should be made very clear that the proposed template is only relevant to integral products. In the case of non-integral products, CE-marking is in place and such a review report is not required.</p> <p>Proposed change:</p> <p>Provide clarification as a first introduction text to the template.</p>	The comment is acknowledged. See comment 826.