EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 April 2022
EMA/CHMP/BWP/QWP/IWG/579239/2021

Overview of comments received on 'Draft Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications' (EMA/CHMP/BWP/QWP/IWG/694114/2019)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Lex Regulatory Limited
2	European Association of Chemical Distributors (FECC)
3	International Society for Pharmaceutical Engineering (ISPE)
4	BioPhorum's Cell & Gene Therapy Phorum
5	The Alliance for Regenerative Medicine (ARM)
6	European Federation of Pharmaceutical Industries and Associations (EFPIA) and Vaccines Europe
7	European Paediatric Translational Research Infrastructure (EPTRI)
8	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
9	Voisin Consulting Life Sciences (VCLS)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Thank you for taking the time to create this comprehensive guidance. I feel it will be highly valuable to organizations developing medicinal products in the context of PRIME.	Comment noted - no response required.
2	How will the PRIME marketing authorisation applications procedure ensure GDPR compliance?	The same provisions apply to PRIME and non-PRIME applications.
3	ISPE thanks EMA for the opportunity to comment on the draft document "Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications." We believe this is a very important document and is, to our knowledge, the first time that a regulatory agency has put into a guidance document the potential science- and risk-based approaches that can be used to accelerate availability of important medicines to patients. ISPE commends EMA for their willingness to publish a toolbox of flexibilities that may be possible for early access programs. We strongly believe that transparency provided by this guideline will lower the perceived barriers for companies looking to accelerate their development and approval of innovative medicines for patients, especially for smaller companies with less regulatory experience. ISPE considers the document to contain an excellent description of the toolbox of flexibilities that may be possible for early access	Comment noted.

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	programs. In particular, we appreciate the clarity provided by the potential flexibilities in use of scientific tools such as *in-silico* models, process validation activities, stability data in the initial filing, and the GMP flexibilities when supported by clear justifications and quality risk management. We further appreciate the clear description of how to engage the Agency in early dialogue. ISPE does, however, recommend that the scope of the document is clarified and broadened. Some suggestions and rationale are given below. ISPE's greatest concern of the document is its appearance of a very narrow scope. The document gives the appearance of being specific to PRIME marketing authorisation applications; the title and Introduction (background) section are specific to PRIME. Yet many of the science- and risk-based approaches that are included in document are applicable to ALL products, and most of the flexibilities discussed may be applicable on case-by-case basis for non-PRIME medicines for unmet medical needs or of major public health interest. While lines 135-137 of the document briefly addresses applicability of the toolbox to non-PRIME early access products, that point can easily be lost in the language of the rest of the document which specifies PRIME. Since all, or nearly all, of the tools discussed are equally applicable to PRIME and early access products on a case-by-case basis when justified, ISPE recommends that the scope of the guideline is broadened and not apparently restricted to only PRIME products. The broadening of the scope would provide consistency with EMA's commitment described in lines 619-623. Such revision would also provide consistency with the	Comment accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.

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	Agency's experience with Conditional Marketing Authorisations of COVID drugs and vaccines, which ISPE understands may have included some of these flexibilities although outside of the PRIME program. ISPE's first recommendation is to change the title, introduction, and scope of the guideline to be reflective of "early access products" rather than "PRIME marketing authorisation applications." Alternatively, the Agency could broaden their access to the PRIME process, especially at the early, proof of principle stage to be inclusive of all early access products. The enhanced dialogue available from the PRIME pathway would benefit sponsors who may have great uncertainties regarding how to balance and optimise the required clinical and safety studies with the necessary quality studies to achieve a good regulatory submission and accelerate availability of these important medicines for patients. ISPE's second recommendation is that the guideline be clarified which tools and sections of the document provide are applicable for all products and which sections contain regulatory flexibilities and thus may be reserved for early access products. Some of the General scientific tools in Section 4.2 (e.g., Prior Knowledge, Risk Assessment, Continuous Process Verification) are not specific to PRIME or early access products; they are simply science- and risk-based approaches consistent with the enhanced development approach described in ICH Q8(R2), ICH Q10, ICH Q11 and ICH Q12. Similarly, the regulatory tool of Post-approval Change Management Protocol (PACMP) discussed in Section 5.4 is not specific to PRIME	The aim of this document is to consolidate in a single document all tools available for medicines that target an unmet medical need. For tools available for all medicines, applicants/MAHs can refer to existing guidance documents (e.g. EMA process validation guidance, EMA Q&A on PACMP, ICH Q8(R2), ICH Q10, ICH Q11 and ICH Q12).

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	products. Lack of clarity about what tools are available for all products vs. limited to PRIME could lead to general misunderstanding about the applicability of the tools. We recommend that the concept of enhanced development tools vs. tools for flexibility be included in the document and clarified for each tool discussed. Thirdly, ISPE recommends that in the Section 5, Regulatory tools section, consideration be given to liaising with other agencies that a sponsor may be approaching to try to align flexibilities being considered for the EU with those of other agencies. Finally, while out of scope for this specific guideline, ISPE suggests that any future revision of EU GMP Annex 15 consider inclusion of some of the clarifications relating to process validation given in this toolbox document. As a worldwide not-for-profit association dedicated to connecting pharmaceutical knowledge to enhance industry efforts to develop, manufacture and reliably deliver quality medicines to patients, ISPE has been actively involved in advancing scientific and regulatory approaches for accelerated development and approvals, such as for PRIME scheme products. Our volunteer members have published several articles on this topic which we will gladly share with EMA, upon request. ISPE encourages EMA to continue dialogue with industry on this topic, either directly with organizations such as ISPE, or through follow-up workshops similar to the regulator-	Comment noted, but this is to be considered on a case-by-case basis and would depend on the feasibility to do it (timings, resources), confidentiality agreements between the agencies and the trade secret restrictions.

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	industry workshop held November 2018, in which the US FDA participated. ISPE does not have line by line edits for the document.	
4	Overall, the review group welcomes the toolbox as a useful development of the 2018 workshop. The collaborative tone applied at the start is encouraging and should be reflected throughout the document. It is crucial for global developers that EMA and FDA continue to work together to align on CMC requirements for expedited programs, in particular for advanced therapies. In this respect the review group encourages a follow-up EMA-FDA joint workshop specifically focused on ATMPs.	Comment noted - no response required.
4	It is noted that in the Scope the Agency states that "It is recognized that some of the tools described in this document may be considered on a case-by-case basis, and prior to agreement with regulators, for other products intended for early access that address an unmet medical need." Not all products targeting unmet needs and with an expedited development pathway have access to, or opt to apply for, the PRIME scheme. Still, the review group agrees with the Agency that the applicability of this toolbox goes beyond products with formal PRIME designation, as CMC issues faced by sponsors for these programs are independent from the designation itself. In order to reflect this, the review group would recommend that the title of the toolbox guideline be adapted to, e.g. "quality considerations to enable early patient access to products with an expedited development targeting unmet medical needs".	Comment accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.
4	Flexibility is much appreciated but there will be some uncertainty for developers in the extent to which the flexibilities can be used and	Comment noted. This is a guidance document. The tools described can be applied on a case-by-case basis

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	the supporting data that might be needed (e.g. which process validation protocols can be post-approval; how representative small-scale processes need to be of commercial scale; level of characterization/qualification for analytical methods for utilising flexibilities). The toolbox does not need to be prescriptive as this could limit flexibility (against the spirit of the document), but the review group are proposing that potential use cases (real or fictitious) be added to improve clarity. These could be presented in an addendum to the guidance to be updated more readily/flexibly and reflecting discussions and case studies presented in workshops.	depending on the product and development approach and data available. Applicants requiring advice on the acceptability of their approach can request scientific advice/protocol assistance from the CHMP: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance. At this point in time it is not feasible to develop case studies. This may be considered for further revisions of the document.
4	While some elements of the toolbox guidance will facilitate acceleration of therapies to patients (e.g. deferral of process validation activities), in general, process and product knowledge affords developers greatest flexibility. Many developers considering PRIME may question the benefit where less flexibility exists with less product/ process knowledge.	In those situations the benefit is in the guidance given on the control strategy in which it is accepted that less process development and understanding information is provided than normally expected, but with a more adapted strategy the product can come to market.
4	Given the specificities of advanced therapies, and the fact that these represent a high proportion of candidates in the PRIME scheme, more examples relevant to ATMP developers would further improve the usefulness of the toolbox.	This document applies to chemical, biological and/or biotechnologically derived substances and ATMPs. It includes some specific references and approaches applicable to ATMPs e.g. 4.7.6. Comparability. For further guidance on the risk/based approach specific to the development of ATMPs, please refer to the dedicated EMA guideline (EMA/CAT/CPWP/686637/2011).
4	One of the biggest challenges for advanced therapy manufacturers, potentially delaying access to breakthrough therapies developed	Comment outside of the scope of this guidance. It is in the remit of the European Commission to start negotiations on a potential scope expansion of an MRA. It should be noted

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	under expedited programs, is in-region testing for ATMPs when these are imported from outside EU. The review group would urge the European Commission/EMA and US FDA to expand the current Mutual Recognition Agreement on batch testing to ATMPs.	that this exercise requires a comparison of legislative and regulatory requirements for ATMP in both regions and these need to be found equivalent. . The possibility to request an exemption from testing upon importation is described in a Q&A document (https://www.ema.europa.eu/en/documents/other/questions-answers-exemption-batch-controls-carried-out-atmps-imported-european-union-third-country_en.pdf).
4	Provision of regulatory and scientific advice during PRIME should be optimised. The toolbox notes the importance of scientific advice as a regulatory tool. Company experiences vary with respect to how flexible, prompt and effective provision of scientific advice has been within the PRIME scheme. For expedited developments it is essential that guidance is provided by the best available experts and in a timely manner when requested. The current SA timelines are often too lengthy, and accelerated timelines should be available when appropriate. Clarifications should not require scientific advice and there should be reassurance for companies that the given advice is ultimately representative of the involved Committees' thinking. There needs to be flexibility considering alignment across regions must be sought on program changes when the program is global. Additionally, it would be assuring for developers to understand if the Agency will play a supporting role to alignment of the timing of quality review (rapporteur) and GMP inspections (local inspector) to facilitate acceleration.	Comment noted. Scientific advices (SA) follow a specific process. There are provisions to accelerate timelines for SA on a case-by-case basis, when justified. Any request is to be discussed in advance with the SA officer. Applicants using the PRIME scheme, can discuss their development program and regulatory strategy with the CHMP/CAT rapporteur and a multidisciplinary group of experts. Scientific advices follow a procedure, involving QWP/BWP, SAWP and CHMP/CAT, as applicable, so all are representative of the Committees' thinking. Applicants can request parallel scientific advice with the EMA and US FDA, as indicated on the EMA website. Interactions with other regulators can take place, when warranted, on a case-by-case basis.
4	Lack of specification guidance: more discussion is needed in the Control Strategy section. Product-specific data related to the control strategy are typically limited at the time of the MAA, and some	Comment noted. In an expedited development program, the product and process knowledge may be limited. For this reason, the control strategy may need to be more stringent

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	suggestions proposed in this section may end up impacting supplies. In particular, where batch experience is limited, limits for specifications, IPCs etc. have to be established on the basis of relevance to the product safety and efficacy, linked to platform/ prior knowledge. Attempting to manufacture with a more constrained control strategy will impact supply to patients. The review group would therefore welcome a dedicated section on specifications reflecting on acceptance criteria wider than available batch data and levels used in clinical trials, if properly justified. Examples of acceptable strategies to justify post-approval changes (for example, dispensation of x OOS batches to allow for broadening range) would also be helpful from a practical perspective.	compared to a standard development in case there are not sufficient supportive data to perform a risk assessment allowing for wider limits, removal of parameter ranges etc. and still guarantee safety and efficacy. A dedicated section related to setting of specifications will be included. See comment below on Control strategy.
4	The guidance on opportunities to update the control strategy (e.g. via PACMPs) is welcome; however, the review group note that in situations of early patient access, the post approval changes required to maintain supply will almost always be substantial and would caution against unnecessary complication of the post approval variations with changes that can be avoided (equally important from a global change perspective).	Comment noted. The more post approval changes can be avoided the better, but changes are sometimes inevitable as the products in accelerated programs will still follow the variation regulations. The need for post-approval changes is to be considered on a case-by-case basis and applicants are encouraged to start making post-authorisation plans well in advance.
4	Maintenance and modernisation of the toolbox will be key moving forward. We need flexible and agile guidance which can be readily adapted to accommodate emerging technologies and evolving global standards. We note in particular that the ICH Quality Discussion Group is working or plans to work on a number of quality guidelines, revising existing tools or introducing new ones. We recommend that	Comment noted - no response required.

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	the toolbox endorse ICH new or revised guidelines relevant to CMC as promptly as possible.	
5	We commend the EMA for the publication of this draft toolbox guidance to support quality data packages for PRIME marketing authorization applications, and we are pleased that the toolbox is applicable to Advanced Therapy Medicinal Products (ATMPs). We welcome the transparency of the Agency on the comprehensive list of tools and the intent to describe where flexibility can be explored. As per a comment below, the Agency should be clear that ultimately all requirements must be met, but that for PRIME products, there is flexibility in the timing and the approach to meet the requirements, which requires welcomed additional dialogue with EMA on CMC elements of the future MAA, including during Scientific Advice. Noting that this guidance was inspired by a joint workshop with FDA, we encourage EMA to continue to pursue international regulatory harmonization or convergence where appropriate on guidance to support quality data packages for products with expedited development, including advanced therapies. The concepts outlined in the PRIME toolbox are excellent candidates for a harmonized regulatory approach, which will facilitate wider and more efficient patient access to life saving therapies, including innovative ATMPs with PRIME. In the US, this should apply to cell and gene therapy products with Regenerative Medicine Advanced Therapy designation or Breakthrough Therapy designation, and to the Sakigake designation in Japan. In this respect we encourage a follow-up EMA-FDA joint workshop specifically focused on ATMPs.	Comment noted - no response required.

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	Also, we would encourage the EMA to use ATMP cluster meetings with FDA to share the toolbox and seek EU-US harmonization in this area.	
5	The scientific tools outlined in this document are particularly helpful for ATMPs. As PRIME ATMPs often have an accelerated development with outstanding clinical efficacy, their benefit-risk profile can be unique, in that they often offer high benefit for patients with urgent medical needs with residual potential risks, such as potential delayed adverse events, requiring long-term follow-up or due to the small patient population studied pre-approval. We agree that benefit-risk profile should be taken into consideration when determining the extent and timing of CMC requirements.	Comment noted - no response required.
5	For ATMPs where a phase III is often not applicable, admission of an applicant or sponsor to the PRIME scheme should not just be driven by company size but also by the type of product. Earlier engagement or application may be beneficial to allow the applicant to fully address scientific advice received. Companies applying for PRIME designation for an ATMP, should be permitted to do so at an earlier time point. This in turn would enable applicants to fully leverage the benefits of the prime tools of scientific advice/meetings.	Comment outside of the scope of this guidance. However, comment will be considered in the context of the ongoing 5-year review of the PRIME scheme.
5	We note that in the Scope the Agency states that "It is recognized that some of the tools described in this document may be considered on a case by case basis, and prior to agreement with regulators, for other products intended for early access that address an unmet medical need." Not all products targeting unmet needs	Comment noted - no response required.

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	and with an expedited development pathway have access to, or opt to apply for, the PRIME scheme. Therefore, we agree with the Agency that the applicability of this toolbox goes beyond products with PRIME designation, as CMC challenges faced by sponsors for these programs are independent from the designation itself.	
5	We commend the EMA for addressing the use of prior knowledge in this document. The use of prior knowledge and the leveraging of platform-based technologies is of particular importance for ATMP's, where a similar technology may be used across several indications or products. We request that the EMA clarify the use of these concepts with additional ATMP examples. The PRIME Toolbox specifically mentions groups of products including monoclonal antibodies, viral vector vaccines or oligonucleotides. We suggest that relevant groups or platforms may also include products such as viral vectors for gene therapy, pluripotent stem cell lines (which are used as starting materials for multiple therapeutics), genome editing tools, and in some cases manufacturing technologies (e.g., non-viral vector approaches). These examples should be included in the PRIME Toolbox document as they would provide further useful guidance for sponsors developing ATMPs.	Comment noted. As indicated in the scope, this guidance applies to medicinal products containing chemical, biological and/or biotechnologically derived substances and ATMPs. The document provides general guidance. Applicants requiring advice on the acceptability of their approach can request scientific advice/protocol assistance from the CHMP: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance. The prior knowledge section lists ATMP examples.
5	PRIME ATMP's are often able to demonstrate significant clinical benefit on an accelerated clinical timeline. This often places process development and CMC related activities on the critical path for product approval. A flexible approach to the timing of these activities is appropriate in order to facilitate the use of the Accelerated Assessment procedure. The concepts outlined in the PRIME Toolbox support this flexible approach, including the use of	Comment noted. The document provides general guidance. The tools described can be applied on a case-by-case basis depending on the product and development approach and data available. Applicants requiring advice on the acceptability of their approach can request scientific advice/protocol assistance from the CHMP: https://www.ema.europa.eu/en/human-

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	concurrent validation, flexibility with respect to stability test requirements, and also the ability to defer some validation activities to a post-authorisation phase. These important concepts would benefit from additional explanation on the circumstances under which they should be applied, including examples.	regulatory/research-development/scientific-advice-protocol-assistance
5	Lack of specification guidance: more discussion is needed in the Control Strategy section. Product-specific data related to the control strategy are typically limited at the time of the MAA, and some suggestions proposed in this section may end up impacting supplies. In particular, where batch experience is limited, limits for specifications, IPCs etc. have to be established on the basis of relevance to the product safety and efficacy, linked to platform/ prior knowledge/ industry experience. We would therefore welcome a dedicated section on specifications reflecting on acceptance criteria wider than available batch data and levels used in clinical trials, if properly justified.	Comment noted. A dedicated section related to setting of specifications will be included. See comment below on Control strategy.
5	Section 4.4.1 describes the strategy of using a more constrained control strategy at the time of approval, until enough data are available to justify a less constrained strategy. This is appropriate in situations where it is desirable to defer certain process development activities to the post market setting, in order to facilitate faster access to the therapeutic for patients. There is an alternative scenario, however, where an applicant has demonstrated sufficient control of their process but may not be able to establish a strong correlation between their release criteria and relevant clinical outcomes. In this case wider release criteria may be warranted in	The level of flexibility should be based on the level of understanding of the impact of the CQAs on the product performance and the link between process parameters and quality attributes. In case it is not possible to establish a correlation between the release criteria (attributes and acceptance criteria) and relevant clinical outcomes due to limited understanding of attribute and process parameter criticality, as a precautionary measure a more stringent control strategy may need to be applied. This is further discussed below in the Control strategy section.

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	order to facilitate patient access. It would be helpful to understand EMA's position on this scenario. Possible examples could include release criteria for appearance and viability.	
5	The guidance on opportunities to update the control strategy (e.g., via PACMPs) is welcome; however, we note that in situations of early patient access, the post approval changes required to maintain supply will almost always be substantial. We recommend that risk management principles should apply to these post-approval changes. As noted in the European Commission/EMA Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management) some principles of ICHQ12 are currently incompatible with the EU Variation. We strongly encourage the European Commission, the EMA and the National Competent Authorities to continue to work on the implementation of the ICH Q12 guideline within the existing EU legal framework, while waiting for a future revision of the relevant legislation	Comment noted – no response required.
5	Maintenance and modernisation of the toolbox will be key moving forward. We need flexible and agile guidance which can be readily adapted to accommodate emerging technologies and evolving global standards. We recommend that the toolbox endorse ICH new or revised guidelines relevant to CMC as promptly as possible.	Comment noted – no response required.
5	One of the biggest challenges for advanced therapy manufacturers, potentially delaying access to breakthrough therapies developed under expedited programs, is in-region testing for ATMPs when these are imported from outside EU. We would urge the European Commission/EMA and US FDA to expand the current Mutual Recognition Agreement on batch testing to ATMPs.	In the GMP guideline for ATMPs there are already some flexibilities with regards to release testing upon importation from third countries. Exemptions can be granted in case there is limited amount of material available (e.g. autologous products) or where the short

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		shelf-life impedes double release testing. The exemption can only be granted if the testing site in the third country is a GMP certified facility, but is in principle not restricted to testing sites in third countries where an MRA with the EU is in place. Comment outside of the scope of this guidance. It is in the remit of the European Commission to start negotiations on a potential scope expansion of an MRA. It should be noted that this exercise requires a comparison of legislative and regulatory requirements for ATMP in both regions and these need to be found equivalent. The possibility to request an exemption from testing upon importation is described in a Q&A document (https://www.ema.europa.eu/en/documents/other/questions-answers-exemption-batch-controls-carried-out-atmps-imported-european-union-third-country_en.pdf).
5	Provision of regulatory and scientific advice during PRIME should be optimised. The toolbox notes the importance of scientific advice as a regulatory tool. Company experiences vary with respect to how flexible, prompt and effective provision of scientific advice has been within the PRIME scheme. For expedited developments it is essential that guidance is provided by the best available experts and in a timely manner when requested. The current SA timelines are often too lengthy, and accelerated timelines should be available when appropriate.	Comment noted. Scientific advices (SA) follow a specific process. There are provisions to accelerate timelines for SA on a case-by-case basis, when justified. Any request is to be discussed in advance with the SA officer. Applicants using the PRIME scheme, can discuss their development program and regulatory strategy with the CHMP/CAT rapporteur and a multidisciplinary group of experts.

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	Clarifications should not require a scientific advice and there should be reassurance for companies that the given advice is ultimately representative of the involved Committees' thinking. There needs to be flexibility considering alignment across regions must be sought on program changes when the program is global.	Scientific advices follow a procedure, involving QWP/BWP, SAWP and CHMP/CAT, as applicable, so all are representative of the Committees' thinking. Applicants can request parallel scientific advice with the EMA and US FDA, as indicated on the EMA website. Interactions with other regulators can take place, when warranted, on a case-by-case basis.
5	As more complex innovative technologies are introduced (e.g., more complex genetic modifications) to address unmet medical needs, we note that the applicability of this toolbox may need to adapt to help address CMC issues at earlier stages of development, potentially prior to PRIME designation. The advancement of various technologies employed for ATMPs these past few years indicate that the number of products that may fall into the category noted in the following sentence "It is recognized that some of the tools described in this document may be considered on a case by case basis, and prior to agreement with regulators, for other products intended for early access that address an unmet medical need," will increase, especially for ATMPs. Therefore, we propose a continuing dialogue to consider how we may be able to better facilitate robust CMC development for these potential future PRIME products with the ultimate goal of enabling early access to patients.	Comment noted – no response required.
5	Comment: Section 5.3, on conditional marketing authorization (CMA) requires some clarification. It implies that in the case of a conditional MA approval, none of this PRIME Toolbox guidance applies, because it states that CMA does not allow an application	Comment noted. The CMA applicability may have been misunderstood by the reader. CMA could be an option for PRIME products

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	dossier that is "less complete than normal" for pharmaceutical (and nonclinical) data. However, the entire premise of this guideline is that the pharmaceutical data may be less complete than normal at the time of MAA and there is no reason to think that the PRIME Toolbox guidance should not apply in the situation of a CMA. In fact, one could argue that it is more relevant in this case, because a CMA is likely to be an early MA and therefore more in need of the flexibilities suggested in the PRIME Toolbox. We refer to our comment on lines 118-119 and would recommend the EMA clarifies that the purpose of the Toolbox guidance is to provide areas of flexibility that allow meeting the requirements to have a complete quality/pharmaceutical data package for marketing authorization over time, as long as it is pre-agreed with the EMA. This includes providing quality/pharmaceutical data during review and post-approval within a defined period. Separately, we would welcome a re-evaluation of the CMA framework to allow for the pharmaceutical data to be less than complete, based on prior agreement, at the time of marketing authorization for complex ATMPs with PRIME designation, understanding that quality specific obligations would be put in place for the CMA to become Full marketing authorization.	(1) which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; (2) to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC; (3) medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000; as described in line with Article 2 Commission Regulation (EC) No 507/2006. According the current EU regulatory framework for a conditional marketing authorisation, a less comprehensive quality dataset is only foreseen for medicinal product to be used in emergency situations. Applicants/MAH are requested not to read this guidance document in isolation, but in the context of the EU regulatory framework.
6	EFPIA and Vaccines Europe (VE) very much welcome the opportunity to provide comments on the draft PRIME Toolbox to EMA. We believe the document is an important step towards accelerating patient access to treatments for unmet medical need;	Comment accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet

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	however, we do have several general and specific comments, which we further detail below. A regulatory decision designating that a product is a PRIME candidate, or not, occurs often too late in the product development process, when key decisions have already been made. The Guidance should therefore allow use of the described tools for all Early Access Programmes including PRIME, Accelerated Assessment and Conditional Marketing Authorisation. It is important to recognise that PRIME is only one of the Early Access Approaches available in the EU (others include Accelerated Assessment and Conditional Marketing Authorisation) and in each case, a pre-requisite is that the products being developed address unmet medical need. We also strongly recommend that the contents of the toolbox be reviewed in the light of learnings from CMC and supply for COVID19. Hence, given the stated scope and importance of this toolbox, industry feels the title should be changed to Toolbox guidance on quality considerations to enable early patient access to products for unmet medical need.	medical need. The document will be revised to make this more clear.
6	In several places, the toolbox makes clear reference to enabling provision of alternative Quality. At several points however, the text refers to accepting "*incomplete data packages*" (e.g. line 214). Industry urges caution in the use of such terminology, noting that approaches described in the toolbox are better reflected as "alternative data packages". We also recommend that phrases such as "*it may be possible under certain circumstances*" need to be	Comment noted. "Alternative quality" is not mentioned in the document. The concern with using terminology such as "incomplete data package" is well taken. "Incomplete data packages" refers to the situation when the submission of certain data is deferred to the post-authorisation phase, as explained in the process validation and control strategy sections.

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	replaced in tone throughout with "*where agreed between applicant and regulators*".	The replacement of "under certain circumstances" by "where agreed between applicant and regulators" is not deemed necessary. Certain (case-by-case) circumstances need to be met to justify the request, that then can be discussed with the regulators to seek agreement. The wording has been revised as reflected in other comments below.
6	Limited manufacturing experience has multiple impacts across many elements of this guidance and approaches for one element (e.g. process validation) needs to be consistent with the other elements e.g. comparability, stability etc.	Comment noted – no response required.
6	We note that there is limited reflection on the specific requirements of ATMPs (such as cell and gene therapies) and urge the Agency to continue discussions with industry on these to develop further considerations	Comment noted – no response required.
6	There is no mention of analytical procedure development and validation in this document; and if/when for example phase-appropriate qualified assays may be used and how best to facilitate changes made to procedures as knowledge increases. It would be useful to address if, for example, qualified assays can be used to file with (with agreement to validate post-approval). In addition, that it is suitable to utilize analytical data which was generated with non-validated assays, providing the correspondence of the qualified and validated assay results can be shown.	Comment noted – In the vast majority of cases it is expected that the analytical methods are validated before approval. Any deviations should be discussed and pre-agreed with regulators. Specific guidance on analytical procedure development and validation is being developed at ICH level (ICH Q2 revision and ICH Q14). This guidance document is an overarching document that summarizes the main regulatory and scientific tools.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		If applicants require specific feedback for their product/strategy they should request scientific advice/protocol assistance.
6	There is mention throughout of "models," but the document lacks a section talking to the role of modelling generally to facilitate early access. For example, there is mention of the use of small scale models in sections 285, 292, 357, 413. It is important to clarify the principles required (e.g., a small scale model needs to be justified as representative, but does not need to be qualified). We recommend an additional section on general principles of use of models to provide additional assurance in lieu of up front quality data/enable deferral of provision of data.	Comment noted. Models can be applied to different areas e.g. small scale models for process evaluation, in-silico models to justify the proposed control of mutagenic impurities, stability models, process models and it is not possible to cover all within this guidance document. If applicants require specific feedback for their product/strategy they are advised to request scientific advice/protocol assistance.
6	There is no mention of considerations for risk-based postponement of importation testing in the EU, which can often be time and resource consuming and wasteful and is considered redundant if repeating identical release testing. Please consider reference to the IFPMA Position paper.	Comment not accepted. Provisions for importation testing in the EU are part of the EU regulatory framework.
6	Industry believes that further development and discussion is required for the section on Control Strategy. Whilst it is clear that product specific data related to the control strategy may be limited at the time of the MAA, industry believes that some suggestions prvesented in this section may have a significant impact on the feasibility of supply. Per the discussions in the 2018 workshop, Statistical tools and batch history cannot be used to establish appropriate specification. Where batch experience is limited and it is vital that limits for specifications, in process	Comment noted. A specific section on setting of specifications has been included. See further comments on aspects related to constrained/comprehensive control strategy below.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	control etc must be established on the basis of relevance to the product safety and efficacy, linked to platform and prior knowledge. Attempting to supply with a more constrained control strategy will impact upon patient supply. Some of the recommendations in this section are logical (e.g. identifying additional CPPs where the potential impact of parameters on CQAs is unclear) but for the most part industry urge EMA to work with industry to revise this section of the toolkit. From our perspective, it would also be beneficial to include an entire new chapter on Specifications in the document.	
6	The sections on stability are considered well-structured and helpful, but would benefit on a further general discussion in the introductory paragraph of science and risk based approaches to stability, applicable to all product types (e.g. reduced studies where justified on the basis of prior knowledge, use of extrapolation and/or data modelling and science and risk-based approaches to the definition of what is a "representative" batch).	Comment partly accepted. See also comment to line 466. A new paragraph has been added.
6	The section on comparability for biologicals is helpful and in particular the references to prior knowledge. Industry also notes per our comments before the 2018 PRIME /BT workshop that considerations of bioequivalence for oral solid dose chemical drugs are also of key importance for early patient access. The workshop and toolkit omitted key discussions between quality and clinical experts on this key scientific tool and, in particular, new scientific methodologies such as in-silico models for IVIVT. We strongly encourage the QWP to engage with industry on this matter and	Comment noted. The toolbox has been developed as a follow up of the workshop. It will be revised as experience is gained.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	refer the Agency to EFPIA's paper of 2020 (Biopharmaceutics Modelling as a Fundamental Tool to Support Accelerated Access).	
6	Regarding the section on regulatory tools industry is disappointed that no reference is made to a number of key points raised at the 2018 PRIME/ BT workshop: • The need for ongoing close engagement and scientific advice in the post approval phase to support the many variations required. • The need for meaningful, rapid and flexible dialogue/scientific advice on GMP matters • No mention of considerations of rolling review Limited reference to reliance and lack of detail on consultative scientific advice with other agencies.	Comment noted. The guidance document refers to tools which are part of the EU regulatory framework. Indeed, scientific advice can also be requested in the post-authorisation phase. To make this clearer the wording has been revised. Scientific advice can be requested in all areas, and the text is not excluding GMP, so no revision is required. Rolling review is not part of the EU regulatory framework.
6	Guidance on opportunities to update the control strategy (e.g. through PACMPs) is welcome. However, industry notes that in situations of early patient access, the post approval changes required to maintain supply will always be substantial and so cautions against unnecessary complication of the post approval variations with changes that can be avoided (e.g. through development of patient centric specifications). The document could therefore benefit from a dedicated section on lifecycle management in general, to ensure post-approval activities are smooth and to some extent covered/addressed in the initial licensing.	Comment noted. PACMPs can be applied during the lifecycle of a product to manage post-approval changes in a flexible manner. These are discussed in the text.
7	The document aims to provide guidance for the preparation of marketing authorisation applications (MAA) of medicinal products that target an unmet medical need (PRIME products). However, reference to the specific requirements needed for developing	Not agreed. The scope of the toolbox or the scope of PRIME does not exclude paediatric medicines. In fact, more than 50% of

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	paediatric medicines as underlined in the Paediatric Regulation and in the many applicable scientific EMA Guidelines are missed and it seems that, in the current form, this toolbox is not applicable to paediatric medicinal products development. Moreover, this is in stringent contrast with the ongoing revision of the Paediatric and Orphan Regulations, that include, among other, the proposal to expand the PRIME scheme application to medicinal products addressing paediatric and rare diseases patients therapeutic needs as a new and important reward to accelerate the access on the market of paediatric drugs. In fact the PRIME scheme should provide adequate paediatric protocol assistance, accelerating drug development phases and implementing innovative study methodologies through paediatric expertise within EMA Committees and Working Parties. Up to December 2019, 33 paediatric drugs (e.g., orphan for inborn error of metabolism, haematology and oncology medicinal products) underwent a fast track approval released by EMA while none addressed the PRIME scheme. This also confirms that the current version of the PRIME scheme is not encouraging in the paediatric setting and that a paediatric specific PRIME procedure should be implemented based on a strong role assigned to the PDCO as Scientific Advisory Working Party evaluating medicines eligible for the paediatric PRIME (this decision could be associated to the PIP evaluation) and guiding PRIME procedure covering preclinical, formulation and clinical phases in line with the provisions in the PIP and involving multiple paediatric expertise in the EMA scientific committees.	products which received PRIME eligibility include a paediatric indication of which 25% concern a paediatric only indication. This guidance document is not to be read on isolation, but together with other available guidance. Specific quality requirements needed for developing paediatric medicines are described in the Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2). Not accepted. Comment out of scope of the guidance. The concept of unmet need in PRIME is wider than the paediatric concept, which therefore is a subset. If the company sufficiently justifies the UMN, these medicines are already included and no specific wording should be needed. Of note, the majority of rejections of PRIME are not due to lack of existence of UMN, but to lack of justification of the potential to address the UMN. However, the key role of the PDCO in the review of paediatric development plans is fully acknowledged. A member of the PDCO is therefore routinely involved in the PRIME kick-off meeting and may be consulted at later

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		stages during the development in case of questions on the PIP and paediatric aspects of the development. Please refer to PRIME - Guidance to applicants (Q&A) (europa.eu) for the involvement of relevant experts from the EU network in the PRIME support scheme including the PDCO.
8	Overall, we welcome the toolbox as a very useful development of the 2018 workshop. It is crucial for global developers that EMA and FDA continue to work together to align on CMC requirements for expedited programs, in particular for advanced therapies as they make up the largest proportion of PRIME products to date. There is little reflection in the current draft on specificities involved in ATMP manufacture. In this respect we encourage a follow-up EMA-FDA joint workshop specifically focused on ATMPs.	Comment noted.
8	We note that in the Scope the Agency states that "It is recognized that some of the tools described in this document may be considered on a case by case basis, and prior to agreement with regulators, for other products intended for early access that address an unmet medical need." Not all products targeting unmet needs and with an expedited development pathway have access to, or opt to apply for, the PRIME scheme. Therefore, we agree with the Agency that the applicability of this toolbox goes beyond products with PRIME designation, as CMC challenges faced by sponsors for these programs are independent from the designation itself.	Comment accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.
8	The toolbox does not need to be prescriptive as this could limit much appreciated flexibility (against the spirit of the document), however we are proposing that potential use cases (real or fictitious) be added to improve clarity. These could be presented in	Comment noted- at this point in time it is not feasible to develop case studies.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	an addendum to the guidance to be updated more readily/flexibly, and reflecting discussions and case studies presented in workshops.	
8	The value of this toolbox would be greatly expanded if concepts in the document were discussed and aligned with other major regulatory authorities (e.g., U.S. FDA). We encourage the EMA to discuss this toolbox at Cluster meetings on ATMPs, as there is a need for additional policy, particularly harmonized policy, in this area. One of the biggest challenges for advanced therapy manufacturers, potentially delaying access to breakthrough therapies developed under expedited programs, is in-region testing for ATMPs when these are imported from outside EU. We would urge the European Commission/EMA and US FDA to expand the current Mutual Recognition Agreement on batch testing to ATMPs.	Comment noted – EMA and FDA were part of the workshop and are collaborating on the topic. Note that this document is not specific to ATMPs. Comment out of scope of the guidance. Currently it is in the remit of the European Commission to start negotiations on a potential scope expansion of an MRA. It should be noted that this exercise requires a comparison of legislative and regulatory requirements for ATMP in both regions and these need to be found equivalent. The possibility to request an exemption from testing upon importation is discussed in a Q&A document (https://www.ema.europa.eu/en/documents/other/questions-answers-exemption-batch-controls-carried-out-atmps-imported-european-union-third-country_en.pdf).
8	Provision of regulatory and scientific advice during PRIME should be optimised. The toolbox notes the importance of scientific advice as a regulatory tool. Company experiences vary with respect to how flexible, prompt and effective provision of scientific advice has been within the PRIME scheme. For expedited developments it is essential that guidance is provided by the best available experts and in a timely manner when requested. The current SA timelines are often too lengthy, and accelerated timelines should be available when appropriate. Clarifications should not require a scientific	Comment noted. SA follow a specific process. There are provisions to accelerate timelines for SA on a case-by-case basis, when justified. Any request is to be discussed in advance with the SA officer. Applicants using the PRIME scheme, can discuss their development program and regulatory strategy with the CHMP/CAT rapporteur and a multidisciplinary group of experts.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	advice and there should be reassurance for companies that the given advice is ultimately representative of the involved Committees' thinking. There needs to be flexibility considering alignment across regions when the program is global.	Scientific advices follow a procedure, involving QWP/BWP, SAWP and CHMP/CAT, as applicable, so all are representative of the Committees' thinking.
8	Maintenance of the toolbox according to scientific and technological progress will be key moving forward. We need flexible and agile guidance which can be readily adapted to accommodate emerging technologies and evolving global standards. We note in particular that the ICH Quality Discussion Group is working on plans to work on a number of quality guidelines, revising existing tools or introducing new ones. We recommend that the toolbox endorse ICH new or revised guidelines relevant to CMC as promptly as possible.	Comment noted – no response required.
8	Admission of an applicant or sponsor to the PRIME scheme should not just be driven by company size but also by the type of product or complexity of development plan. Earlier engagement or application may be beneficial to allow the applicant to fully address scientific advice received. Timing of application for the PRIME enrolment should be considered earlier for ATMPs. This in turn would enable applicants to fully leverage the benefits of the prime tools of scientific advice/meetings.	Comment noted but out of scope of this guidance. Comment will be considered in the context of the ongoing 5-year review of the PRIME scheme. Notably, admission of the PRIME scheme does not depend on the company size except for early entry cases based on non-clinical data and clinical tolerability data, which is limited to academic institutions and SMEs. Please refer to relevant guidance for applicants on the PRIME scheme which covers the program features.
9	VCLS welcomes the initiative from the EMA to implement flexibility in the quality requirements at the time of MAA for products that have entered the PRIME scheme. VCLS also welcomes the related guidance, currently under public consultation.	Comment noted – no response required.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The content of the guidance, presented in two main sections: "scientific tools" and "regulatory tools" is user-friendly.	
9	The "scientific tools" section (section 4) is very comprehensive and the introduction of the notion of "prior knowledge" very welcomed.	Comment noted – no response required.
9	The "regulatory tools" section (section 5) is less comprehensive and refers to existing ways to expedite the development and marketing authorization. It could be made clearer in the document that the listed procedures are not specific to PRIME products.	Comment noted. Regulatory tools section has been included to indicate that the regulatory tools already exist and are part of the EU regulatory framework and not limited to PRIME products.
9	Based on the above comments, it is not clear to which extent the initiatives included in the guidance are specific to PRIME products?	Comment noted. As indicated in the executive summary, this toolbox summarizes 'scientific elements and regulatory tools, available in the existing EU regulatory framework, that can be applied to support the development and completion of Module 3 quality data packages in the preparation of MAA of designated PRIME medicinal products'. This document should not be read in isolation, but together with related legislation and guidance documents.
9	The "scientific tools" sections discuss potential level of flexibility without distinction between product type (NCE, Biologics, ATMP). The level of acceptable flexibility may be different depending on product complexity and discussion on the applicability of the proposed tools for each product types would be welcome. For example, the use of validation protocols as substitute for validation results is usually well accepted for NCE but prone to higher challenges for biologics or ATMP. If feasible, tabulated details on the applicability of the proposed scientific tools for each product	Comment noted. The applicability of the tools would also depend on the specific product and its development program. Applicants should consider this guidance in the context of their product & development program. If they have questions they can request product-specific scientific advice.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	types and specific expectations would be helpful to complete the proposed guidance.	
9	The "scientific tools" discussion does not currently discuss potency assays which represent an important challenge in the framework of accelerated development as they often take time to develop and validate and require orthogonal approaches. We recognize the availability of specific guidelines discussing potency but guidance on expectations in the framework of accelerated development would be welcome.	Comment outside of the scope. The toolbox is not aimed at discussing the different types of assays.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Title	6	Industry notes and supports the clear intent (line 136) that the applicability of this toolbox goes beyond products with formal PRIME designation. In order to reflect this intent, industry suggests that the toolbox title be adapted to reflect this, Proposed change: *"Toolbox guidance on quality considerations to enable early patient access to products for unmet medical need*".	Comment accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
67	6	Industry notes (lines 69) the Executive Summary refers to scientific elements and tools available in the EU network related to data requirements for the MAA module 3. The guidance also contains significant additional information on Quality beyond the MAA (e.g. on GMP, site licensing and regulatory tool and processes) which should be reflected in the Summary Proposed change (if any): From "*This document provides guidance, in a 'toolbox approach', by summarising scientific elements and regulatory tools, available in the existing EU regulatory framework, that can be applied to support the development and completion of Module 3 quality data packages in the preparation of marketing authorisation applications (MAA) of designated PRIME medicinal products.*" To *"This document provides guidance, in a 'toolbox approach' by summarising scientific elements and regulatory tools, that can be applied to support the development and supply of new therapies and vaccines for unmet medical need".*	Comment noted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear. Manufacturing sites are part of Module 3, so their registration is covered by the existing wording. Although some of the regulatory tools described (e.g. CMA) are not quality specific, the guidance document is, and this should be clear to the reader. Therefore, the text is kept as it is.
70	6	The scope of this guidance is significantly broader than module 3 in MAAs. **Proposed change:** This document provides guidance, in a 'toolbox approach', by summarising scientific elements and regulatory tools, available in the existing EU regulatory framework, that can be applied to *support product and control strategy development, GMP manufacture and supply, and the provision of quality data for clinical trials, marketing authorisation applications (MAA) and post approval changes of designated products for unmet medical need.*	Comment not agreed. The scope of this guidance document is Module 3, which also covers sites registration. The proposal is beyond the scope of the actual document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
78 - 98	6	Consistent with the later text in Section 1. Background (Introduction) which focuses on Early Access Approaches the text on the specifics of the PRIME mechanism should be minimised with reference being made to applicable Guidance. Additionally, reference should be made to other Regulatory approaches for Early Access (Accelerated Assessment and Conditional Marketing Authorisation) consistent with their inclusion in Section 5.0 (Regulatory Tools). The Executive Summary should be adjusted accordingly. **Proposed change:** "The European Medicines Agency (EMA) launched the PRIME scheme to support the development of medicines that target an unmet medical need. PRIME is based on enhanced interaction and early dialogue between agency and industry to optimise development and accelerate MA review, so that these medicines reach patients earlier. See http://ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines for further information on the PRIME scheme. PRIME complements other Regulatory approaches for Early Access (Accelerated Assessment and Conditional Marketing Authorisation) as described in http://ema.europa.eu/en/documents/leaflet/early-access-medicines-development-support-regulatory-tools-en.pdf and http://ema.europa.eu/en/human-regulatory/overview/support-early-access."	Comment partially accepted. References will be added. Text will be maintained as is and complemented with a reference to other early access tools as proposed.
82-83	9	It is stated that PRIME is granted to products that has shown its "potential to benefit patients with unmet medical needs based on early clinical data". However, in the PRIME guidance from the EMA, applicants from the academic sector and SMEs can submit earlier, based on "compelling non-clinical data and tolerability data from initial clinical trials".	Partly accepted. The statement applies to both PRIME requests based on data supporting clinical proof of concept and early entry requests based on non-clinical and clinical tolerability data. Agreed to add some clarification as follows:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change : "To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data or non-clinical data and tolerability data from initial clinical trials for academic and SME applicants".	*Line 83: In exceptional cases, PRIME designation may also be granted to applicants from the academic sector and micro-, small-and medium-sized enterprises (SME) at an earlier stage of development based on non-clinical data and first in man studies indicate adequate exposure and tolerability.*
82-83	7	In the process of identification of proposal adequate to access to the PRIME scheme, the PDCO has to have a crucial role with reference to the paediatric ones to guarantee that all the needs are recognised. **Proposed change :** To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Regarding the paediatric proposals, they have to be evaluated by the Paediatric Committee (PDCO) to assess the eligibility.	Not accepted. Comment out of scope of this guidance. . Please refer to PRIME - Guidance to applicants (Q&A) (europa.eu) for details on the PRIME eligibility review process. Review of PRIME eligibility requests will be conducted through the SAWP. Please note that SAWP includes members of the PDCO. Please also refer to the Paediatric Regulation which sets out the role of the PDCO in the centralised procedure, specially its role in the assessment of the content of paediatric investigation plans (PIPs).
84 - 88	2	Would EMA be able to provide what will be the selection process in appointing the rapporteur selected for PRIME?	The Rapporteur appointment for PRIME products is conducted in line with the Procedural Advice

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): /	on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) No 726/2004.
85-86	7	It is important that also paediatric needs and criticism have to be taken into account and care. A strong role of the PDCO as Scientific Advisory Working Party has to be considered to evaluate medicines eligible for the Paediatric PRIME (this decision could be associated to the PIP evaluation) and guiding a 'Protocol assistance' procedure. **Proposed change (if any):** Appoint a rapporteur from the from the Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy and from the Paediatric Committee (PDCO) in the case of a paediatric indication	Not accepted. Comment out of scope of the guidance. However, the key role of the PDCO in the review of paediatric development plans is fully acknowledged. A member of the PDCO is therefore routinely involved in the PRIME kick-off meeting and may be consulted at later stages during the development in case of questions on the PIP and paediatric aspects of the development. Please also refer to PRIME - Guidance to applicants (Q&A) (europa.eu) for the appointment of rapporteurs and the involvement of relevant experts from the EU network in the PRIME support scheme including the PDCO. Please also refer to the Paediatric Regulation which sets out the role of the PDCO in the centralised procedure, specially its role in the assessment of the content of paediatric investigation plans (PIPs).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
89 – 91	2	When will the meeting be conducted, and would this be open to select stakeholders or to the general public?	The kick off meeting is a multidisciplinary meeting between the PRIME applicant and the CHMP/CAT Rapporteur, the EMA product team and a multidisciplinary group of experts from the relevant EMA scientific committees and working parties and is conducted after his product is accepted into the PRIME Scheme.
91	7	Include the PDCO rapporteur among the rapporteurs of the kick-off meeting. **Proposed change (if any):** Organise a kick-off meeting with the CHMP/CAT/PDCO rapporteur	Not accepted. A member of the PDCO is routinely involved in the PRIME kick-off meeting. The involvement is covered in the current guidance by reference to a multidisciplinary group of experts.
106 - 108	6	The sentence should reference comparability. It is also noted that "specification setting" is listed, though there is no specific discussion on release specification and the stability section has no discussion on qualifying an end of shelf-life specification on the basis of limited manufacturing and clinical experience. **Proposed change:** Specific guidance includes product characterisation, specification setting, comparability, validation and stability testing as well as early identification of quality issues / attributes that are critical to the clinical use of the medicinal product.	Comment accepted. Comparability is added to line 106. Revision is made and specification setting and shelf-life determination are discussed under the control strategy and stability sections.
113	6	" *applicants should ensure that manufacturers are compliant with EU GMP and are inspection ready at the time of submission*"	Comment accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Refer to section 4.5. See comment on that section and how EMA will assess EU GMP compliance for each manufacturing site using all available tools *applicants should ensure that manufacturers are appropriately compliant with EU GMP and are inspection ready at the time of submission (see section 4.5)*	
118-119	5	It is not clear how regulatory tools can support timely access if the product quality requirements for marketing authorization must be consistent with current legislation (2001/83/EC as amended). We suggest making it clear that the ultimate requirements for product quality to obtain marketing authorization in the EU must be in line with Annex I of 2001/83/EC, using a risk based approach where appropriate (EMA/CAT/CPWP/686637/2011), but that a Sponsor can leverage the PRIME Toolbox scientific elements and regulatory tools to have some flexibility as to when this goal of meeting all Annex I requirements must be met. The Agency should also consider modifying lines 214, 215, and 216 accordingly. The Agency could also be clear that some of the tools and flexibility described in the guidance could apply to situations of health emergency but that this is not the scope of this guidance.	Comment noted. This information is already included in lines 118-125. Section risk assessment The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.
120	6	*'The data needed to demonstrate quality, safety and efficacy in line with 120 Annex I of Directive 2001/83/EC is expected to be provided in the MAA dossier'*	Comment noted. For the approval of a medicine the applicant should provide sufficient data to demonstrate its quality. This may be by

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change add: *'…or post approval, to a plan presented in the dossier'*	providing all the data as such, or for certain element(s) present a PACMP to be agreed with regulators, that may allow the deferral of some data generation. The text as it is does not exclude this possibility..
125	9	The description of platform data and, for ATMP, the notion of risk based approach is being introduced with a reference to Annex I, part IV of Directive 2001/83/EC. **Proposed change:** include Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products as it also addresses risk based approach and the notion of flexibility	AcceptedThe reference was included under section 3 and will be added to the references section: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.
132-134	7	The involvement of the PDCO is fundamental to guarantee the paediatric needs are covered. **Proposed change:** The scope of this document is on medicinal products that have received PRIME designation by the CHMP and includes medicinal products containing chemical, biological and/or biotechnologically derived substances and Advanced Therapy Medicinal Products (ATMPs). In case of a paediatric indication, the preliminary opinion of PDCO is collected.	Not accepted. Comment out of scope of the guidance. However, the key role of the PDCO in the review of paediatric development plans is fully acknowledged. A member of the PDCO is therefore routinely involved in the PRIME kick-off meeting and may be consulted at later stages during the development in case of questions on the PIP and paediatric aspects of the development. Please also refer to PRIME - Guidance to applicants (Q&A) (europa.eu) for the involvement of relevant experts from the EU

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			network in the PRIME support scheme including the PDCO.
135	6	The text implies only certain tools may be applicable to those medicines being developed outside of PRIME. We see no specific scientific or technical reason why a particular tool described in this guidance could/should only be applicable to medicines for early access for unmet medical need progressed under the PRIME scheme. A serious limitation is that the scope applies when PRIME has been designated yet the tools described would need to be in place by the Applicant early in development, before PRIME is granted by CHMP. **Proposed change:** Replace 132-137 with *The scope of this document for medicinal products containing chemical, biological and/or biotechnologically derived substances and Advanced Therapy Medicinal Products (ATMPs). The tools described in this document may be considered on a case by case basis, via agreement with regulators, for products intended for early access that address an unmet medical need.*	Comment partially accepted. The draft toolbox already acknowledges that the scientific elements and regulatory tools described in this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME products which also address an unmet medical need. The document will be revised to make this more clear.
154-155	7	Almost the more relevant Paediatric Guidelines should be listed. **Proposed change:** Please add the following guideline to the list: EMA/CHMP/QWP/805880/2012 Rev. 2 - Guideline on pharmaceutical development of medicines for paediatric use.	Comment not accepted. This document should be read in conjunction with all the other guidance available. We are only listing the main ones which generally apply to all products. We cannot list all guidance that may apply.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
161	9	Guideline on process validation for finished products – information and data to be provided in the regulatory submission (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1) is cited in Section 3 "Legal and regulatory basis" **Proposed change:** Include the Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission EMA/CHMP/BWP/187338/2014 as it brings important information specific to biologics.	Comment not accepted. That reference was already included in the draft version published for consultation.
167	6	We propose to add as reference: EMA QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC	Not accepted. The flexibilities used during COVID-19 pandemic may not be applied to medicines for an unmet medical need.
176-223	8	Could EMA clarify what is defined as "lower level of GMP" for starting biological material. Are there recognized levels that are still considered GMP? Is there clear separation between those levels, what are their attributes or is the determination made on a case by case situation based on risk assessment for a given material.	Accepted. Replace "low level of GMP" in the title and the text with "appropriate level of GMP".
177	5	We appreciate the chapter on prior knowledge. At the same time more clarity would be needed to help companies to start capturing relevant prior knowledge in some formalized way. For example, in the case of different viral vectors manufactured using an established platform, when could stability data from a different vector using the same platform be leveraged? We understand that it may be hard to introduce specific examples (with contexts) or case studies of what can be used as prior knowledge, and as platform information. Could the Agency elaborate more on how similar processes would have to be to leverage prior knowledge?	Not accepted. An in depth discussion on Prior Knowledge is outside the scope of the Toolbox Guidance. It is also outside the scope to give examples of how similar processes have to be in order to leverage Prior Knowledge. It is up to each Applicant to justify that the process(es) from which Prior Knowledge is leveraged are sufficiently similar in order to leverage the data.

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		Also, the examples are focused on prior knowledge in manufacturing, but there may be other areas where prior knowledge could be applied. As an example, there may be significant prior knowledge of principle molecular features of a cell or gene therapy that may be leveraged across programs as a "platform."	
177	6	The section on Prior and Platform knowledge is very clear and impactful. Industry notes the EMA comment on making "*reference to previous* filings" (line 191) in the MAA which industry believes is a significant step forward which will facilitate the appropriate summary of presentation of relevant prior knowledge in the MAA. (H) Industry also notes recent proposals shared by EMA on the development of "platform technology master files" (see EMA/CVMP/IWP/582191/2020) which could be of significant benefit in simplifying development activities and regulatory submissions. **Proposed change:** Consider including section on platform technology master files per EMA/CVMP/IWP/582191/2020.	Not accepted. The concept of Platform Technology Master Files relates to the legislation governing veterinary medicinal products and is currently not part of the legislation governing medicinal products for human use.
177-201	8	The discussion of use of prior knowledge is helpful and would be even more useful if expanded to specifically address how a sponsor's prior knowledge may apply in cell and gene therapy development, e.g. for cell therapies, where starting material is considered highly variable, enrichment steps are frequently highly specific orthogonal techniques where cells are selected by virtue of specific density and cell surface markers achieving purification factors akin to monoclonal antibodies purification processes. Therefore, some of the challenges of the more heterogenous material are alleviated by such a platform, and outputs of such platform processes	Comment noted. However, a detailed discussion on platform approaches for individual product classes is beyond the scope of the document.

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		are comparable and can be leveraged for ATMPs. For example, such platforms could be applicable to both: gene-modified cell therapies and their corresponding raw materials or drug substances such as viral vectors and gene editing tools (CRISPR/Cas9, plasmids encoding Transcription activator-like effector nucleases (TALEN) or Zinc finger nucleases, and RNA). The viral vectors or gene editing processes could be platform processes as they would have very similar up- and downstream processes including formulation, stability, storage, primary container closure. Similarly, a gene-modified cell therapy platform that consistently uses the same cell phenotype and corresponding enrichment and cultivation approach could also be considered a platform, especially if affinity steps such as enrichment for cell surface markers are employed. **Proposed change:** Line 198/199 include cell therapies if the same cell type & purification/enrichment process is used	
181-182	9	The introduction of the notion of prior knowledge as part of the scientific tools that could be leveraged to justify the amount of quality data at the time of MAA is welcome. Whilst it is acknowledged that MAA is applicant/product-specific and this prior knowledge should not be restricted to the product's developer's knowledge, the balance/mix between "product-applicant own data / prior-well established knowledge" for the different components of the MAA file should be mutually agreed upon between EMA / Applicant. **Proposed change:** "Prior knowledge includes ~~company~~ knowledge from development and manufacturing experience […]"	Accepted.

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184	6	We suggested that a line should be added about specialist manufacturer's experience counting as prior knowledge. The report from the 2017 workshop on prior knowledge (EMA/CHMP/BWP/187162/2018) talks to internal knowledge from a company and the company's historical experience. Whilst leveraging a specialist manufacturer's experience hasn't been called out specifically. **Proposed change** after line 184: *'An applicant working with a 3rd party modality/platform expert manufacturer, can also present evidence of that expertise which can be used to support the development and validity of a manufacturing process or control.'*	Partially accepted. Text changed to state "Prior knowledge includes ~~company~~ knowledge from development and manufacturing experience". The intent is not to restrict Prior Knowledge to the particular Applicant. Prior Knowledge from e.g. a CMO can also be presented by an Applicant.
185	6	Alternative approaches can be justified, as well as timing. It might be helpful to illustrate here what could be in the scope of the quality studies which can leverage from prior knowledge. **Proposed change:** "The availability of prior knowledge, if demonstrated to be relevant for the product in question, could be good basis for shifting the ~~time-point~~ approach for completion of certain quality studies (e.g. stability studies, Process validation, justification of specification etc)."	Accepted. Proposed change: The availability of prior knowledge, if demonstrated to be relevant for the product in question, could be good basis for shifting the time-point of for completion of certain quality studies, or changing the approach to certain quality studies (e.g. stability studies, process validation, justification of specification etc.).
188-193	5	In order to ensure that ATMP's are covered by this section, change the term "molecule" to "product"	Accepted

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		Proposed change: "If the knowledge is not related to experience with the product in question, but based on a similar product, then the applicability of the knowledge to the new product needs to be justified, and the knowledge also needs to be communicated in the dossier for the new product …"	
194	6	**Proposed change:** (to align with previous EMA guidance and best practise): *"Prior knowledge information should be included in the CTD in the section where the product specific information otherwise would be, or as appropriate in the manufacturing process development sections together with ~~argumentation~~ justification on how the information is relevant"*	Accepted.
195-196	7	Prior knowledge may make some developmental studies redundant. However, additional studies could be necessary in case of an ad hoc paediatric formulation. **Proposed change:** To be added: However it should be specified if prior knowledge is also relevant for the planned paediatric formulations.	Not accepted. The current sentence is quite general. It is generally understood that Prior Knowledge needs to be justified for each formulation. There does not appear to be a need to single out paediatric formulations or other types of formulations.
198	5	Include some ATMP specific examples. Suggest examples could be manufacturing equipment, PSC cell lines, and viral vectors. **Proposed change:** Examples of such groups can include monoclonal antibodies, viral vector vaccines, viral vectors for gene therapy, oligonucleotides, PSC cell lines (which are used as starting materials for multiple therapeutics), genome editing tools, and manufacturing equipment for non-viral vector transfection.	Comment accepted. Prior knowledge can also stem from "platforms", which means that, for example, similar formulation, manufacturing process and/or analytical testing is used across many different ~~molecules~~ products within a group. Such groups can include monoclonal antibodies, viral vector

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			vaccines, mRNA vaccines, viral vectors for gene therapy, expression vector system (e.g. Baculovirus expression vector system), genetically-modified cell therapies, or oligonucleotides. It is up to the applicant to justify that their product forms part of their platform.
198	6	Suggestion to add other well established or future vaccines production platforms. **Proposed change:** *"Such groups can include monoclonal antibodies, viral vector vaccines, expression vector system (e.g. Baculovirus expression vector system), mRNA or oligonucleotides."*	Accepted. See previous comment
198-201	5	Suggest that specific information to clarify what qualification means in practical terms would be useful e.g., is the provision of a detailed comparative description and data from other products (and platform) a potential expectation for Module 3 content? **Proposed change:** For example: "In such cases the number of products already included in the platform and other information on the extent of knowledge available, together with information on the qualification of the new molecule to the platform is essential in order to assess the applicability of the platform. Information required in Module 3	Partially accepted. A summary of the combined process performance data for multiple product may comprise an enormous dataset, such a large amount of data is not obligatory for justifying that the product fits the platform. To provide detailed guidance on qualification data requirements is beyond the scope of this document.

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		may include comparative descriptive details for all the products for which data is used and a summary of the combined process performance data for the platform."	
198-201	8	"*In such cases the number of products already included in the platform and other information on the extent of knowledge available, together with information on the qualification of the new molecule to the platform is essential in order to assess the applicability of the platform*." Could the Agency clarify what qualification means in this context and which type of data would need to be submitted to demonstrate it.	Partially accepted. A summary of the combined process performance data for multiple product may comprise an enormous dataset, such a large amount of data is not obligatory for justifying that the product fits the platform. To provide detailed guidance on qualification data requirements is beyond the scope of this document.
202-223	8	This Section Risk assessment just references to EMA/CAT/CPWP/686637/2011 for ATMPs. The EMA CAT guidance is out-dated and does not take a decade of additional experiences including several marketed products and lessons learned into account. Risk based approaches for ATMPs should be re-considered in the context of these lessons learned including but not limited to: Platform and prior knowledge approaches to mitigate risk Raw materials and addition of or replacement of vendors and establishing comparability based on risk Use of healthy donor material and/or surrogate materials such as representative cell lines as surrogates to assess process changes for ATMPs.	Not accepted. The Toolbox Guideline is not the appropriate Guideline to provide updated guidance on risk based approaches for ATMPs.

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		Proposed change for line 222/223: Expand this section to provide more up to date details on risk and platforms for ATMPs and/or consider updating of the 2011 guidance for more clarity.	
208-210	6	Add in sentence to state risk assessment can also be used to assess attribute criticality, models used to evaluate manufacturing processes, stability etc and inform on the control strategy **Proposed change:** *"With the use of the identified risk profile the applicant shall justify the extent of data available in the various sections of the MAA dossier. Risk assessments are also used to evaluate dossier elements such attribute critically, the shelf-life, appropriateness of models and prior knowledge and to inform the overall control strategy".*	Partly accepted. Proposed change This tool is typically used as part of the pharmaceutical development to evaluate the formulation and manufacturing processes to understand the impact of material attributes and process parameters on product quality, define their criticality and inform the studies to be conducted. Risk assessments are also used to evaluate dossier elements such attribute critically, appropriateness of models and prior knowledge and to inform the overall control strategy. Formal risk assessment approaches generally have limited use for setting the shelf life, and therefore this aspect was omitted from the revised text.

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212 - 216	6	On two occasions (line 214, line 676, the toolbox makes clear reference to enabling provision of alternative Quality approaches to justify the quality, safety and efficacy of the product (prior knowledge, stability etc) which is strongly supported by industry. In some cases, however, the text refers to "*incomplete data packages"* (e.g. line 214) at time of approval. Industry urges caution in the use of such terminology, noting that approaches described in the toolbox are better reflected as "alternative" data packages". Many of the proposed approaches justify deferral provision of conventional data by providing alternative supporting data. Residual risks are mitigated through e.g. commitments. The final dossier will contain more information (alternative and conventional) than the standard dossier (e.g. biologic stability has modelling information and conventional long-term data). **Proposed change:** "The potential risk resulting from the replacement of certain conventional data by alternative supporting data and mitigations such as commitments ~~incomplete data packages~~ at time of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA review and the augmentation of the final data package post-approval."	Partly accepted. The concern with using terminology such as "incomplete data package" is well taken. However, it is not agreed to include reference to "commitments" as a risk mitigation measure since there is no legal basis for "commitments" in the EU. In the EU, several pathways exist for provision of data post-approval e.g. Specific Obligation, Annex 2 condition, Recommendation etc. Propose to reword as follows The potential risk resulting from ~~incomplete~~ the replacement of certain conventional data by alternative supporting data packages at time of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA review.
214	8	The concept of risk-based approach should be reinforced and linked to the evidence generation and further alignment with National level activities – this may be linked to CMA tool.	Not accepted. The specific proposal for amending the text is not clear. It is not clear how risk based approached should be further aligned with national level activities.

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214-216	5	From 118-119 above Current language seems to imply that it is possible to be approved without meeting the requirements set in Annex I, which is not aligned with line 118 and 119. We suggest adding a reference to providing additional data during review or post-approval starting on line 216. **Proposed change:** The potential risk resulting from incomplete data packages at time of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA review and this risk based approach can lead to agreement in providing additional quality data during review or post-approval if the clinical benefits clearly outweigh the risks.	Accepted. Proposed change The potential risk resulting from ~~incomplete~~ the replacement of certain conventional data by alternative supporting data packages at time of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA review. This risk based approach can lead to agreement in providing additional quality data during review or post-approval if the clinical benefits clearly outweigh the risks.
217-219	5	Application for PRIME is voluntary and not all products intended to meet an unmet need apply. The level of residual risk could be the same for PRIME and some non-PRIME products. Suggest to delete this paragraph or revise the wording. **Proposed change:** Risk-based approaches may also be applicable for non-PRIME products. The level of residual risks that can be accepted will reflect the extent to which a product meets an unmet clinical need. (e.g. it is more likely to accept a lesser degree of assurance for a life-saving product compared to a product where well-documented, usable alternatives exist).	Partially accepted. The level of residual risk could be the same for PRIME and some non-PRIME products that address an unmet medical need, not all non-PRIME products.
217-219	9	It is understood that in therapeutic area with unmet medical need, the "level or residuals risks" that can be accepted can be higher than where alternatives exist.	Accepted. Wording revised.

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		However, this is not restricted to PRIME products (though targeting an unmet medical need is part of the eligibility criteria); and there are plenty of non-PRIME products that still target an unmet medical need for which the RBA and flexibility can apply. **Proposed change:** ~~Although~~ risk-based approaches may also be applicable for non-PRIME products~~, it is worth noting the difference, i.e. that the level of residual risks that can be accepted for non-PRIME products compared to PRIME products (~~which are intended for an unmet clinical need: the level of residual risks that can be accepted for such products (whether that have PRIME or not) may be lower (e.g. it is more likely to accept a lesser degree of assurance for a life-saving product compared to a product where well-documented, usable alternatives exist).	
218-220	6	This section implies that only PRIME products address unmet medical need. The section should be revised to focus on product that address diseases proportionate to medical need (e.g.,….accepted for non-PRIME products compared to PRIME products (which are intended for an unmet clinical need). **Proposed change:** Although many risk-based approaches are ~~may~~ also applicable for products eligible for early access approaches (including non-PRIME products), it is worth noting the difference, i.e. that the level of residual risks that can be accepted for ~~non-PRIME~~ products eligible for early access approaches compared to ineligible ~~PRIME~~ products), may be lower (e.g. it is more likely to accept a lesser degree of assurance	Accepted. See comment above for proposed change

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		for a life-saving product compared to a product where well documented, usable alternatives exist).	
224-335	8	This Section Process validation should be further clarified to indicate if the reduction in batch requirements is a consideration for all products, e.g. small batch sizes for blood, tissue or cell derived ATMPs as they often lead to a wealth of batches and manufacturing experience while process validation with surrogate material is often necessary. A combinatorial approach where applicable clinical manufacturing experience and prior knowledge/platform can be leveraged to potentially reduce the number of required batches for process validation. At the same time, a gain in efficiency for either starting materials or final products e.g. viral vectors, or gene editing tools is also desirable. Manufacture of a full set of process validation batches for these materials can lead to waste if these commercial batches exceed material requirements post approval. Lastly, where formulation platforms and storage conditions are leveraged and prior knowledge not only within the company but across the industry and scientific field is fully supportive of shelf life, the requirements around established storage and shipping conditions of cells or vectors in liquid nitrogen or at -70/-80C should allow to drive a reduced validation package in terms of batches to place on stability as well. It should also be further clarified if section 4.3.1, Process validation protocols, could be leveraged for ATMPs to provide details on planned concurrent process validation to further bolster the number of patient derived material batches produced and what advantages this would bring (e.g. reduction in number of batches) as compared to receive a quality requirement to provide the data post approval. Further distinction from section 4.3.2 Concurrent validation is also needed which speaks to the same reduction in batches and use of a validation master plan as well as sign off by the Qualified Person as compared to the protocol approach. Neither	Not accepted. In Section 2 Scope, it is clearly indicated that the scope of the Guideline applies to ATMPs. Therefore it is not considered necessary to single out blood, tissue or cell derived ATMPs in individual sections. The purpose of the Process Validation tools is not to "potentially reduce the number of required batches for process validation" as suggested by the comment, but rather to defer when the data can be provided i.e. pre-approval or post-approval. The number of batches required to convincingly demonstrate that the process is in a validated state will always depend on the type of product and the demonstrated process knowledge. Where the manufacture of process validation batches would exceed commercial batch requirements, a concurrent process validation approach could be considered. In such cases, the

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		section makes it sufficiently clear if these approaches could be leveraged for ATMPs and the required framework. As noted in the section 4.3.2, this approach also increases GMP inspection complexity. While it is appreciated that successful PRIME applicants can leverage the benefits of scientific advice for more clarification on how this could be managed, additional clarification on impact for e.g. a previously established multiproduct facility on use of prior knowledge/platform approaches to facilitate a GMP inspection with a concurrent validation scheme would also be beneficial. If this is considered to fall under 4.3.5. Continuous process verification, that should also be further clarified. Definitions for the terms in the context of the PRIME scheme and toolbox would be beneficial. **Proposed change:** Provide additional clarity on the vision and feasibility of these approaches for specific products, incl. ATMPs. Provide clear definitions and boundaries of the different validation combined validation/verification scheme including overlap, if any. e.g. line 242/243 include specific products / ATMP examples	batches are commercialised concurrently with process validation. Comments pertaining to stability are discussed further in Section 4.6 *Scientific tools related to stability* As stated above, the entire Guideline is applicable to ATMPs and the purpose of the Guideline is not to reduce the requirement in the number of process validation batches. Details of how to facilitate a GMP inspection are outside the scope of this Guideline. Definitions for the terms will be provided.
229	6	It is not a general requirement at present to provide process validation batch data in the MAA and nor is 3 batches a general expectation at present. Also, this section would benefit from clearer consideration of when well understood manufacturing processes for established biological platforms (e.g. some mAbs) could be considered "standard". Also, is "PPQ" an EU term?	Partly accepted. The following sentence is included in line 227 to make it clear that the entire section covers those cases where PV data is required prior to approval:

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		We note the wording in Guideline for process validation for finished products EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 which states *"In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier at the time of regulatory submission, for example when the product is a biological / biotech product or where the applicant is proposing a non-standard method of manufacture (see section 8 and Annex II). In these cases, data should be provided in the dossier on a number of consecutive batches at production scale prior to approval. The number of batches should be based on the variability of the process, the complexity of the process / product, process knowledge gained during development, supportive data at commercial scale during technology transfer and the overall experience of the manufacturer. Data on a minimum of 3 production scale batches should be submitted unless otherwise justified. Data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and a justification as highlighted above."* We also note the additional wording in EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 which states "*According to section 5.1, full production-scale data should be provided in the dossier for non-standard products or processes which were validated using traditional process validation. It is possible for the applicant to justify that the product process can be considered standard for a particular manufacturer / site taking into account the risk to the patient of failure of the product or process."* Proposed change:	The tools below describe flexibilities for products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes).

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		From: "*departure from the traditional requirement of data from a minimum of three process performance qualification (PPQ) batches can be accepted by regulators when there is a strong benefit/risk of the product in question"* To "*Where it is currently considered necessary to provide production scale validation data in the marketing authorisation dossier at the time of regulatory submission, (for example when the product is a biological / biotech product or where the applicant is proposing a non-standard method of manufacture) an applicant can propose an alternative approach where there is a strong benefit/risk for the product in question. The number of batches for process validation should be justified on the basis of risk assessment"*	
231	7	A flexible approach is considered in the toolbox in the validation process of data available prior of the approval, if a strong risk/benefit exists. However, risk/benefit could be very different for children respects the adults population. **Proposed change:** To be added: The benefit/risks evaluation to the aim of a more flexible process validation should take into account the paediatric risk/benefit specificity.	Not accepted. Benefit risk decisions always take the intended patient population into account. Highlighting particular patient populations in the guideline is not necessary.
239	9	EU GMP Annex 15 is mentioned in the context of process validation protocols **Proposed change:** include Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products as it also addresses the topic of process validation and potential approaches to consider for ATMP	Accepted. Proposed change: A process validation protocol, also known as a process validation scheme, is a plan describing what data will be gathered and how it will be

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			analysed (see EU GMP Annex 15, Guidelines on Good Manufacturing Practice specific to advanced Therapy Medicinal Products, and CHMP process validation guidelines).
240	6	concurrent validation is helpful and supported. However, there is misleading text: *"Normally it is expected that most validation activities are finished at the time of MAA…"* In our view, this is not correct. It is not a requirement of standard synthetic products to have completed validation at the time of MAA filing, and protocols are typically supplied for Product manufacture. Such requirement is not typical for non-sterile active substances or standard manufacturing processes. **Proposed change:** *In cases where normally it is expected that most validation activities are finished at the time of MAA ~~but~~ even today certain validation protocols are accepted as substitutes for a final validation report."*	Accepted. Proposed change In cases where it is normally ~~it is~~ expected that most validation activities are finished at the time of MAA ~~but~~ and process validation data included in the MAA dossier, in exceptional circumstances certain validation protocols are accepted as substitutes for a final validation report.
243	5	*"For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process validation activities to the post-authorisation phase and submit protocols for the studies to be performed and their acceptance criteria. The scope of validation protocols could be expanded to include other validation activities, for example hold time studies, transport validation, reprocessing etc."* Could the Agency clarify what about these examples makes them a good candidate for deferral to the post-authorisation phase? With more clarity on the rationale sponsors would have more opportunities to identify activities that could be proposed for deferral.	Accepted. Proposed change: For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some ancillary process validation activities to the post-authorisation phase. ~~and submit protocols for the studies to be~~

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		As an example, the provision of protocols for validation studies such as transportation qualification and hold time studies could be proposed in lieu of data from these studies.	~~performed and their acceptance criteria.~~ Protocols could be submitted in lieu of supportive validation data prior to approval. The protocol should include the studies to be performed and their acceptance criteria. The scope of validation protocols could be expanded to include other validation activities outside of the main PPQ study, for example hold time studies, transport validation, reprocessing etc.
243-247	8	*"For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process validation activities to the post-authorisation phase and submit protocols for the studies to be performed and their acceptance criteria. The scope of validation protocols could be expanded to include other validation activities, for example hold time studies, transport validation, reprocessing etc."* Could the Agency clarify what about these examples makes them a good candidate for deferral to the post-authorisation phase. With more clarity on the rationale sponsors would have more opportunities to identify activities that could be proposed for deferral.	Accepted For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process validation activities to the post-authorisation phase. ~~and submit protocols for the studies to be performed and their acceptance criteria.~~ Protocols could be submitted in lieu of validation data prior to approval. The protocol should include the studies to be performed and their acceptance criteria. The scope of validation protocols could be expanded to include other validation activities outside of the main PPQ study, for example hold time studies, transport validation, reprocessing etc.

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249-251	9	in the context of using validation protocols as substitute to validation report, it is mentioned that "Contrary to post-approval change management protocols (PACMPs) (see section on 250 regulatory tools), process validation protocols are not followed by an implementing variation as they cover aspects already described in the dossier". **Proposed change:** provide information regarding the expected timing of submission for the validation data: prior to approval? to launch?	Accepted. Proposed change: ~~Contrary to post-approval change management protocols (PACMPs) (see section on regulatory tools), process validation protocols are not followed by an implementing variation as they cover aspects already described in the dossier.~~ For these type of process validation protocols, provided that the results are in accordance with the agreed protocol, submission of the data post-approval is not a requirement. This is in contrast to post-approval change management protocols (PACMPs), where a subsequent variation is required before implementing the change.
253	5	Suggest to add the ATMP GMP guideline reference	Accepted Proposed change: Concurrent validation is defined in Annex 15 of the EU Guidelines for GMP as validation carried out in exceptional circumstances, justified on the basis of a strong benefit-risk ratio for the

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			patient, where the validation protocol is executed concurrently with commercialisation of the validation batches. Similarly, as described in the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, concurrent validation may be acceptable where there is limited availability of the starting materials and/or where there is a strong benefit-risk ratio for the patient.
255	6	Industry welcomes the section on concurrent validation and supports that concurrent validation should be used as a fundamental tool to enable early patient access. We urge the EMA to further clarify this section in order to further enable the appropriate and much needed use of concurrent validation (e.g. by clarifying clearly that early patient access for unmet medical need is clear an example of the Annex 15 "exception circumstances" **Proposed change:** *"Concurrent validation is defined in Annex 15 of the EU Guidelines for GMP as validation carried out in exceptional circumstances, justified on the basis of a strong benefit-risk ratio for the patient, where the validation protocol is executed concurrently with commercialisation of the validation batches. Situations of unmet medical need may be considered as exceptional circumstances, and concurrent validation an important tool to enable early patient access. If concurrent validation is proposed, it….."*	Partially accepted. *Situations of unmet medical can fall under exceptional circumstances. Applicants are encouraged to liaise with regulators to ensure there is common understanding on the specific case.*

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256-257	7	In the concurrent validation, the needs of patients has to be taken into account as the benefit/risk balance. The fragile populations require a special attention in order to guarantee that effectively their needs will be addressed. **Proposed change:** If concurrent validation is proposed, it should be appropriately justified based on patient need, and its acceptance will depend on the benefit/risk balance. A special focus, should be done considering the fragile population like paediatric one. It should also require the involvement of patients representatives and patients organisations.	Not accepted. It goes beyond the scope of the Guideline to highlight every patient population for which the use of concurrent validation may be justified. Patient representatives may have the opportunity to comment during CHMP, however mandating that this must take place for every discussion on current validation is considered too restrictive.
269 - 271	5	"the tests registered in the protocol should include all relevant in-process controls and process parameters to support a conclusion that any given batch of product will be uniform" – suggest that in addition to ensuring uniform is that it demonstrates the process has performed as expected, and the quality of the product is consistent. **Proposed change:** "the tests registered in the protocol should include all relevant in-process controls and process parameters to support a conclusion that any given batch of product will be consistent"	Accepted. Proposed change: In addition to the release specifications, the tests registered in the protocol should include all relevant in-process controls and process parameters to support a conclusion that the process has performed as expected and any given batch of product will be ~~uniform~~consistent
277	5	Suggest that "verify" might not be a suitable word in this context. **Proposed change:** "…the control strategy will properly assure that the process has performed as intended"	Accepted Proposed change the control strategy will properly ~~verify~~ assure that the process has performed as intended"

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283-293	5	Suggest to add clarification for any batches proposed to support process performance with respect to the expectations for analytical methods used (including analytical method performance) and quality attributes which were assessed. And any subsequent method changes or additional tests (quality attributes studied) which might make confirmation of process performance against the final control strategy challenging. **Proposed change:** For example, add: "Where the data from non-PPQ batches is proposed to support process validation, the test methods used to analyse these batches should provide data equivalent to the results from PPQ batch(es). Therefore, consideration should be given to method performance and the quality attributes studied."	Partly accepted. It is agreed that method performance should be considered. However using the word "equivalent" in this regard could be misinterpreted as having a strict statistical meaning e.g. an equivalence test. Proposed change: Where available, data from other non-PPQ batches (including clinical batches) manufactured using the commercial manufacturing process can be used as supportive data to justify that the process is in a state of control. Where data from non-PPQ batches is used to support process validation, consideration should be given to method performance and the quality attributes studied. If the non-PPQ batches were tested using methods different from the registered commercial analytical methods, this should be justified.
287	6	There is inconsistency detailing of the requirements for process validation. As written, line 287 implies that provision of data in the MA from at least one validation batch data is always an expectation. This is not correct (e.g. for standard, non-sterile manufacturing processes).	Accepted Propose to include the following sentence at line 227 to make it clearer:

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		Line 297 is more accurate as written: "*products where process validation data would normally be required prior to approval (e.g biological products, chemical products manufactured using a non-standard process),…"* **Proposed change:** ~~It is generally expected that data from at least one formal process validation batch from the commercial manufacturing process will be available prior to approval. *In exceptional cases,*~~ *For products where process validation data would normally be required prior to approval it may be acceptable not to have ~~successfully~~ manufactured any PPQ batches prior to approval*.	The tools below describe flexibilities for products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes).
287 – 290 293 297 - 306	5	Inconsistent detailing of the requirements for process validation, first part of the section is asking for validation data 'it is generally expected that data from at least one formal process validation batches from the commercial process will be available prior to approval' and provision of interim process validation data during MAA review is also desirable. And then from 297 onwards, 'for products where process validation data would normally be required prior to approval (e.g., biological products, chemical products manufactured using a non-standard process), the data from the concurrent process validation batches should be submitted post approval. Requirements need to be clear on what the expectations are for submission of concurrent validation data for standard and non-standard/ biological products, e.g., the data from the concurrent process validation batches can be submitted post approval.	Accepted. Propose to include the following sentence at line 227 to make it clearer: The tools below describe flexibilities for products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes). Also propose to delete the same text from lines 297 to 298, as it is causing confusion, see next comments. Proposed change: ~~For products where process validation data~~

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			~~would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes),~~ ~~the~~ Data from the concurrent process validation batches should be submitted post-approval.
from line 290	4	Guidance states that in exceptional cases, it may be acceptable not to have successfully manufactured any PPQ batches prior to approval. The review group dislike use of the word successfully in this context since it may be interpreted that either of two possibilities would be acceptable i.e. it may be possible not to conduct any PPQ batches prior to approval or it may be possible to submit data from failed PPQ runs. **Proposed change:** The review group would therefore recommend alternative, less ambiguous language.	Accepted. Propose to delete the word "successfully": In exceptional cases, it may be acceptable not to have ~~successfully~~ manufactured any PPQ batches prior to approval.
297	4	Sentence starts "For products where process validation data would normally be required prior to approval". Per standard product life cycle approach, the review group would expect that process validation data would be required for all products prior to approval, **Proposed change:** To apply this toolbox, the review group would recommend use of examples to highlight these exceptional circumstances (or cross reference to other relevant examples within the guidance as appropriate).	Partially accepted. Process validation data is not required for all products prior to approval. For example, process validation from full scale commercial batches is not required to be included in Module 3 for non-sterile chemical active substances and for chemical medicinal products manufactured using standard processes .

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			Line 227 now includes the following statement to make this clearer: The tools below describe flexibilities for products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes)
297 - 301	6	The paragraph is not clear as it has two sentences staring with "However" in succession that are near contradiction and could be misunderstood. The proposed change simplifies the text with the same message. **Proposed change:** *For products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes), the data from the concurrent process validation batches should be submitted post-approval. ~~However~~, Formal regulatory approval will generally not be required for release of concurrent validation batches to the market unless otherwise communicated to the applicant. ~~However, depending on the benefit-risk ratio evaluation, formal regulatory approval could be required for release of concurrent validation batches to the market~~*	Accepted. Proposed change: ~~For products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes),~~ ~~the~~ Data from the concurrent process validation batches should be submitted post-approval. ~~However,~~ Formal regulatory approval will generally not be required for release of concurrent validation batches to the market, unless otherwise determined during assessment as being necessary based on the benefit-risk evaluation. Any decision on the requirement for formal regulatory approval for release of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			concurrent validation batches will be communicated to the Applicant prior to MA approval. ~~However, depending on the benefit-risk ratio evaluation, formal regulatory approval could be required for release of concurrent validation batches to the market.~~ Footnote added :"Additional requirements apply to products under Official Control Authority Batch Release (e.g. vaccines, plasma derived products)"
299-302 309-311	9	This paragraph is difficult to follow. It is explained earlier that it is expected to have at least one formal PV batch from the commercial manufacturing process prior to approval, but here is mentioned that data for the concurrent process validation batches should be submitted post approval. Finally, here is described a mixed approach where some PV data could be available prior to authorization and other data provided post approval. **Proposed change:** provide clarification and examples of situations whereby the different scenarios described could be considered. Would it be applicable to any product type including ATMP? What are the circumstances that will help justify deferral of submission of PV results?	Partly accepted. It will normally be expected that data from one PPQ batch is available prior to approval with data from concurrent PV batches provided post-approval Proposed change to line 297 - 302 ~~For products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes),~~ ~~the~~ Data from the concurrent process validation batches should be submitted post-approval. ~~However,~~ Formal regulatory approval will

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			generally not be required for release of concurrent validation batches to the market, unless otherwise determined during assessment as being necessary based on the benefit-risk evaluation. Any decision on the requirement for formal regulatory approval for release of concurrent validation batches will be communicated to the Applicant prior to MA approval. ~~However, depending on the benefit-risk ratio evaluation, formal regulatory approval could be required for release of concurrent validation batches to the market.~~ Proposal to address comments on 309 – 311: Aside from concurrent validation, it may be possible ~~under certain circumstances~~ to defer certain process validation activities to the post-approval phase. This would allow for a mixed approach where some process validation data are available prior to authorisation and other data is provided post-approval. Some examples include, but are not limited to, transport validation, column lifetime validation, hold time validation, validation of reprocessing etc.

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301	6	In the case of concurrent validation, it is noted that the formal regulatory approval of batch control data prior to release may, under specific circumstances, be requested. Where this is the case, it is important that the evaluation of these data is timely to avoid delay in supply. It is recommended to outline when the" *need for formal regulatory approval of batch control data prior to release*" would be communicated to the Applicant. The draft guidance should also clarify how concurrent validation data would be provided (both when requiring and when not requiring formal approval) e.g. through a Recommendation, Specific Obligation or as an Annex II condition. **Proposed change:** We recommend that detail is provided on how the need for regulatory approval prior to release to the market would be communicated and that commitment procedures to provide it are clearly defined to avoid delay in supply.	Accepted Proposed change: Data from the concurrent process validation batches should be submitted post-approval. ~~However,~~ Formal regulatory approval will generally not be required for release of concurrent validation batches to the market, unless otherwise determined during assessment as being necessary based on the benefit-risk evaluation. Any decision on the requirement for formal regulatory approval for release of concurrent validation batches will be communicated to the Applicant prior to MA approval.
301-302	5	Suggest to clarify whether this approach could be feasible for autologous products.	Not accepted. In Section 2 Scope, it is clearly indicated that the scope of the Guideline applies to ATMPs. Therefore it is not considered necessary to single out autologous products in individual sections.
308-309	5	Suggest clarifying what is meant by "certain process validation activities" (aside from concurrent validation) and "under certain circumstances" by way of examples.	Accepted

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			Agreed that "certain circumstances" is ambiguous Proposed change Aside from concurrent validation, it may be possible ~~under certain circumstances~~ to defer certain process validation activities to the post-approval phase. This would allow for a mixed approach where some process validation data are available prior to authorisation and other data is provided post-approval. Some examples include, but are not limited to, transport validation, column lifetime validation, hold time validation, validation of reprocessing etc.
From line 308	4	Guidance states that it may be possible under certain circumstances to defer certain process validation activities to post-approval phase and this flexibility is welcomed. Proposed change (if any): As a minor comment, the review group felt that it may benefit the reader to cross reference prior section 4.3.1 Process Validation protocols (row 244 which states "For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process validation activities to the post-authorisation phase").	Partly accepted Proposed change Aside from concurrent validation, it may be possible ~~under certain circumstances~~ to defer certain process validation activities to the post-approval phase. This would allow for a mixed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			approach where some process validation data are available prior to authorisation and other data is provided post-approval. Some examples include, but are not limited to, transport validation, column lifetime validation, hold time validation, validation of reprocessing etc.
308-309	8	"*Aside from concurrent validation, it may be possible under certain circumstances to defer certain process validation activities to the post-approval phase.*" It would be helpful to have examples of these circumstances.	Accepted Proposed change Aside from concurrent validation, it may be possible ~~under certain circumstances~~ to defer certain process validation activities to the post-approval phase. This would allow for a mixed approach where some process validation data are available prior to authorisation and other data is provided post-approval. Some examples include, but are not limited to, transport validation, column lifetime validation, hold time validation, validation of reprocessing etc.
308-313	5	Suggest this is an area of focus and potentially rate-limiting for ATMPs (and other products) so propose that additional guidance would be valuable. For example, advice on the justification of batch number, the use of batches from scaled-down	Not accepted.

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		models and batches manufactured at other sites and the status of analytical method validation (and absence of certain tests).	A discussion the number of batches and scale down models etc. for ATMPs is outside the scope of this Guideline
315-316	5	Suggest clarifying what is meant by "under certain circumstances" by way of examples.	Not accepted. The guidance is a toolbox, it is not possible to describe all possible circumstances. Proposed change: In order to avoid delays in finished product PPQ activities, it may be acceptable~~, under certain circumstances,~~ to manufacture and supply finished product PPQ batches using active substance batches which were produced prior to formal active substance process validation, provided the active substance batches were manufactured under GMP and controlled under GMP in full accordance with the applied manufacturing process. If this approach is chosen, it should be demonstrated that such active substance batches are sufficiently representative of the commercial manufacturing process and will meet their intended specifications ~~for quality and purity~~.
316-319	8	*"In order to avoid delays in finished product PPQ activities, it may be acceptable, under certain circumstances, to manufacture finished product PPQ batches using active substance batches which were produced prior to formal active substance*	Accepted. Proposed change:

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		process validation, provided the active substance batches were manufactured under GMP." It would be helpful to have some examples demonstrating these circumstances in a non-limiting way (i.e. "including but not limited to…".	In order to avoid delays in finished product PPQ activities, it may be acceptable~~, under certain circumstances,~~ to manufacture and supply finished product PPQ batches using active substance batches which were produced prior to formal active substance process validation, provided the active substance batches were manufactured under GMP and controlled under GMP in full accordance with the applied manufacturing process. If this approach is chosen, it should be demonstrated that such active substance batches are sufficiently representative of the commercial manufacturing process and will meet their intended specifications ~~for quality and purity~~.
316-321	5	Suggest to clarify the expectations for the methods used and the status of these methods e.g., if not all batch release (specification) methods were available for testing the active substance batches used for drug product PPQ or if methods were subsequently modified.	Not accepted. This is adequately covered by the text "If this approach is chosen, it should be demonstrated that such active substance batches are sufficiently representative of the commercial manufacturing process and will meet their intended specifications for quality and purity". Part of the justification for the batches being sufficiently representative will include a

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			justification around the batch testing and analytical methods used.
317	6	The section on "decoupling" substance and product validation (Line 314) is unclear. Currently it is normal practise to support Product validation with API from various sources. The innovation discussed in the 2018 Workshop was to enable the commercial supply of Product manufactured from non-validated API produced under appropriate GMP (e.g. for clinical or stability studies). **Proposed change:** *"…may be acceptable, under certain circumstances, to manufacture and supply finished product PPQ batches using active substance batches which were produced prior to formal active substance process validation, provided the active substance batches were manufactured under GMP."*	Accepted. Internal comment. Propose to accept since normally companies are allowed to market PPQ batches. I don't think we would forbid a company from marketing DP PPQ batches because the DS batches used were manufactured prior to formal validation. Proposed change: provided the active substance batches were manufactured and controlled under GMP in full accordance with the applied manufacturing process.
322	6	This section is welcome. However, its is noteworthy that the principles of CPV are applicable to the earlier sections on protocols, deferred data and concurrent validation. **Proposed change:** We suggest this section be move to earlier in the validation section so the principles described it can help frame the whole section.	Not accepted. Since continuous process verification (using extensive in-line, on-line or at-line controls) has rarely been proposed by industry, it is arguably not as impactful as the other tools described and therefore it seems appropriate to leave as the last tool in this section.

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From 323	4	Review group would consider both process validation + CPV to be conducted as general practise. Choice of language used in the guidance suggests that CPV can be used instead of process validation. **Proposed change:** Some additional clarity would be appreciated if this is not the intention.	Not accepted. The comment may be misinterpreting CPV as ongoing process verification (referred to as CPV by FDA), rather than continuous process verification which uses extensive in-line extensive in-line, on-line or at-line controls. Continuous process verification has rarely been used by Applicants to date, and therefore is not considered as general practice. The text is indeed intended to convey that continuous process verification can be used instead of "traditional" process verification. As stated in the EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014): "continuous process verification in which manufacturing process performance is continuously monitored and evaluated is an alternative approach to traditional process verification".

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333-335	5	Suggest to provide advice as to additional considerations for highly complex products such as ATMPs and whether it might be feasible to use a verification (only) approach.	Not accepted Providing additional advice on continuous process verification for ATMPs is outside the scope of this Guideline.
337	6	The section on a "more constrained control strategy" needs significant review and revision. The section as written reflects existing prevailing thinking of batch data driving elements of the control strategy rather than science, risk based, patient centred development based on available efficacy and safety data. This section should clarify that the proposed control strategy should be be supported by the available data and risk-based justification. Setting a narrow window of control based on limited data set risks safe and efficacious product being manufactured outside of the constrained control strategy considering that the knowledge of process capability may be limited at the time of filing. This may lead to shortages rather than accelerated access for patients. **Proposed change:** L337, amend title to '4.4.1 Control strategy at initial filing' and see subsequent comments	Not accepted. In an expedited development the product and process knowledge may be limited. For this reason, the control strategy may need to be more stringent/more comprehensive compared to a standard development as there are not sufficient supportive data to perform a risk assessment allowing for wider limits, removal of parameter ranges etc. and still guarantee safety and efficacy. As discussed throughout the document the extent of the control strategy is dependent on the level of knowledge from the applicant
337	6	Proposed changes: We recommend that a specific and important section on "specifications" is introduced which reflects discussions and outcomes from the 2018 workshop with a focus on what to do when there are few batches produced with a limited number used in clinical trials with which to develop specification limits? In such scenarios, statistical tools and batch history cannot be used to establish appropriate specification limits were batch experience is limited and it is vital that limits for specifications, in process control etc must be established on the basis of	Accepted. Text to cover setting of specifications will be included as follows. **Setting of specifications** It may be possible to establish specification acceptance criteria/limits which are wider than

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		relevance to the product safety and efficacy, linked to platform and prior knowledge. We note that the principle of narrow specification limits, widened after more data is available, will significantly impact supply and should not be a feature proposed in this guidance. Rather the guidance should address: • That available batch data at time of MA may not capture the normal manufacturing variability • The high risk of OOS results if specifications are set based on limited numbers of batches, and the risks of rejection of quality material. • That acceptance criteria wider than available batch data and wider than the levels used in clinical trials can be agreed • That prior knowledge and/ or in-vivo/ in-vitro model data can be used to address risk of adverse effects and establish specification acceptance criteria for biological products That there needs to be adequate justification of proposed limits (i.e. not high level or vague) that justifies how the limits will result in safe and efficacious medicines, and how such justifications should elements such as, Prior and platform knowledge, In vitro data, Data from dose finding studies. Industry notes the helpful points made by Sean Barry of HPRA in the presentation at the DIA Europe meeting 15-19 March 2021, slide 12.	the release data of batches used in clinical studies. In this case, the limits should still be appropriately justified in terms of clinical impact (i.e., product knowledge as it relates to safety and effectiveness). Importantly, additional sources of information beyond clinical experience are always considered when establishing specifications for any program, not just PRIME. However, it is recognised that setting specification acceptance criteria wider than clinical experience is frequently required specifically for PRIME programs. Such additional sources of information could include, but are not limited to, *in vitro* data, animal data, published information, prior knowledge specific to a development platform, ,and the impact of potential critical quality attributes (CQA) from related development programs. In using information from other products, a comparison, and justification for any differences between products should be provided. This comparison can, include, for example, context of use (e.g., dosage forms, dosing regimens, route and duration of drug administration, clinical

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			indications, and the intended patient populations), chemical characteristics, mechanism of action, analytical testing, manufacturing processes, formulations, and container closure systems. The justification specification limits for CQAs should be linked to clinical performance rather than solely derived from statistical methods such as tolerance intervals. Statistical analysis on limited number of batches could result in specification limits which are too broad and cannot be justified clinically.
337	6	**Proposed change:** Reference should be made to the stability section that refers to back calculation for the release specification when extrapolation of stability data has been used (488). However, guidance is absent for those CQAs that do not change over time under the recommended storage condition.	Accepted. A reference to the stability section has been included in the proposal above.
337-414	8	This Section, Constrained control strategy, specifically advises more testing and tighter boundaries for the control strategy to accelerate process development. From a manufacturer's perspective, this approach carries a high risk of design out of the optimum process performance window. Combining of a lack of knowledge with a tighter control strategy and an increased testing and control regimen can lead to the realization that the process has been controlled into an operating range that's suboptimal for clinical performance once clinical data are matched to process and release data. If this restrictive control strategy carries into the pivotal study	Not accepted. See justification above. In case of lack of sufficient process understanding, it will not be possible to design the optimal control strategy and the risk to set a control strategy away from its true optimum must be higher when insufficient background data is at hand. Comment on front loading of control strategy noted.

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		manufacturing process and the process control strategy is incorrectly set, away from its true optimum, it becomes extremely difficult and costly to change. Section 4.4.3 Frontloading of control strategy development. This could be an attractive approach in the context of platform/prior knowledge approaches where a set of non-critical process parameters and to some extent attributes is already well known. However, at a success rate of less than 15% in phase I this front loading of risk lacks commercial and financial viability. **Proposed change:** In general, add a paragraph on risk in the preamble of this section lines 225-236. 4.4.1 paragraph 264-274, speak to examples for ATMPs.	Proposed change is not related to control strategy. Lines 225-236 is the introduction to the process validation section and 264-274 on concurrent validation..
348-352	5	Suggest for autologous products this could result in an increased risk of out of compliance/out of specification batches and associated challenges. Therefore, a comment on specific considerations and potential approaches for these types of products would be useful. **Proposed change:** For example, add "careful considerations should be given to the potential implications for the approach taken e.g., for patient-specific products such as autologous products, to assure that measures are in place, consistent with current guidance, to decide the best course of action for the patient in the event of a batch which is out of compliance and/or out of specification."	Accepted.
360-367	6	References to "constrained" control strategies should be made with care. In many cases, it may not be practical to manufacture with overly narrow parameter ranges in the absence of specific data on impact. Narrowing ranges could make it challenging to produce batches consistently and also confine the manufacturing	Partly accepted. The proposed deletion of relax or de-constrain is accepted. The wording for line 364-366 is revised as follows: "Once suitable data has been gathered post-approval, an appropriate variation could be submitted to revise the commercial final control

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		space unnecessarily. Based on a platform process, companies should be able to the use prior knowledge in combination with robust testing to support ranges. Consideration of the overall control strategy should be made in assessing risk. **Proposed change:** ~~*"Ranges of process parameters could also be narrowed until data is available showing that a wider range of process parameter inputs does not impact the relevant critical quality attributes (CQAs) outputs of that manufacturing step.*~~ *In the absence of product specific data on parameter ranges or criticality, relevant prior knowledge from similar products and processes can be used to justify the selected parameter ranges if appropriately justified and considering the overall control strategy.* *Once suitable data has been gathered post-approval, an appropriate variation could be submitted to revise* ~~*"relax" or de-constrain*~~ *the control strategy e.g. downgrade/remove critical process parameters, reduce testing requirements, update analytical procedures, widen parameter ranges etc.*	strategy "e.g. downgrade/remove process parameters, widen ranges, etc. " The deleted text starting line 360 needs to be retained in case relevant prior knowledge does not exist.
365	4	Guidance indicates once suitable data a variation could be submitted to "relax" control strategy. **Proposed change:** The review group would recommend that use of an alternative terminology "'correctly position with more data" may be more appropriate.	Accepted. Point taken Proposed wording: Once suitable data has been gathered post-approval, an appropriate variation could be submitted to revise the commercial final control strategy ~~"relax" or de-constrain the control strategy~~ e.g. downgrade/remove process parameters, widen ranges etc.

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367	6	Guidance on opportunities to update the control strategy (e.g. through PACMPs) is welcome. However, industry notes that in situations of early patient access, the post approval changes required to maintain supply will always be substantial and so cautions against unnecessary complication of the post approval variations with changes that can be avoided (e.g. through development of patient centric specifications). Further information is sought on how changes to the control strategy could be enabled via tools such as PACMPs post approval. Industry note the significance in enabling ongoing supply of facilitating changes to elements of the control strategy such as specification limits , removal of tests, reclassifying parameters as non-critical etc. Industry also note the key role that PACMPs can play in such changes. However, we encourage EMA to further elaborate on how PACMPs can be used in this manner. **Proposed change:** *The process evaluation data required to support the ~~relaxing~~ revision of a control strategy could be agreed during the initial assessment phase as part of a PACMP."*	Partly accepted. Wording will be added to describe how PACMPs can be used to support revising the control strategy.. The proposed change to delete "relaxing" can be accepted. Taken together the text will read: Once suitable data has been gathered post-approval, an appropriate variation could be submitted to revise the commercial final control strategy e.g. downgrade/remove process parameters, widen ranges etc. The process evaluation data required to support the revision of a control strategy could be agreed during the initial assessment phase as part of a PACMP."
370	5	The section on The acceptance and use of in-silico models and purge factor calculations needs clarification on whether it applies to all product types, or only to those types that are in ICH M7 scope (e.g., it would not be applicable to biologics which are not in scope for M7).	Partly accepted. It is probable that most applications of this section will be in the context of chemically synthesised molecules. However, chemical synthesis of parts or fragments of biologics could apply and the use of in-silico models and purge factors calculations for this purpose may be envisioned.

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			ICH M7 foresees the use of in-silico models in the control of mutagenic impurities and defines four potential approaches to the development of a control strategy (section 8.1), where option 4 is relies on understanding of process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification). *The concept of in-silico models and/or purge factor calculation may also be applied when chemical synthesis is used to manufacture larger molecules out of scope of ICH M7 (e.g. antibody drug conjugates).* ~~*(Or would we prefer not to go into this detail? Would this be correct for both in-silico models and purge factors? It may be easier to say that it does not apply to biologics.)*~~
371	4	The review group recommend defining "purge factor".	Not accepted. The comment is acknowledged. However, this is an existing term not unique to this guideline and is to be understood by the reader.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(Purge reflects the ability of a process to reduce the level of an impurity, and the. purge factor is defined as the level of an impurity at an upstream point in a process. divided by the level of an impurity at a downstream point in a process.)
371	8	This section needs clarification on whether it applies to all product types, or only to those types that are in ICH M7 scope (e.g. it would not be applicable to biologics which are not in scope for M7).	See above comment in line 370.
371	9	The applicability of in-silico models and purge factor calculation for complex biologics like ATMP should be clarified	See above comment in line 370.
371-372	5	Suggest to add another section to advise on the scenario where studies to confirm clearance of process-related impurities (or certain product-related impurities) have not been performed (and suitable analytical methods might not be available). For example, to advise on how calculations for theorised worse-case clearance might be used with safety assessments to justify the proposed absence of impurity testing. For gene therapy ("gene transfer") products, this would seem to be a divergence from Ph Eur 5.14 with respect to certain process-related impurities i.e., validate clearance or test, so advice on the robustness of an approach which diverges from this would be valued.	Not accepted. Only high-level advice can be provided. It is not possible to address many specific scenarios in a guideline, also considering the variety of topics being covered. An attempt to give guidance on this issue is not seen as in-line with the general level of information in the document.

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		Proposed change: For example, add a section with the title "The acceptance and use of clearance calculations and safety assessments to justify the absence of impurity tests"	
371-408	6	The use of modelling in this section is limited to impurities. Consideration should be given to other possible application of models in the document to support early patient access including (but not limited to) PK models to justify CQA's/CMAs, mechanistic modelling of manufacturing processes (e.g. to to predict CPP's moving from small to commercial scale) **Proposed change:** Agency to work with EFPIA experts to draft an additional section on general principals of use of models to provide additional assurance in lieu of up front quality data/enable deferral of provision of data.	Not accepted. The comment is acknowledged and may be covered in future documents but is considered out of scope for the present revision. It is proposed not to include PK models and mechanistic modelling of manufacturing processes at this stage.
399 - 408	6	The section on purge considerations for the control of impurities is welcome. However, it is also not clear that this aligns to the stated position in the draft ICH M7 Q&A document and the text may be more representative of views expressed after the workshop and specific to purge calculations for N Nitrosamines. Industry has published multiple papers showing the applicability of Purge Calculations and a recently published industry survey has shown that close to 70% of MIs are controlled based on an option 3 / 4 approach with acceptance from authorities. . Industry note the comments made on the importance of transparency on programs and algorithms used for purge calculations. Key aspects such as purge ratios and even system design (Mirabilis) and access have been actively pursued by industry and Lhasa to explain and address any regulatory concerns.	Not accepted The inclusion of nitrosamine calculations is not accepted at this point as EMA in their guidance documents has not yet accepted purge calculations for nitrosamine impurities due to incomplete information on the data used to support the calculations. The Toolbox Guidance does include references to regulatory guidance documents but not scientific publications and it is proposed not to include a direct reference as suggested.

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		Proposed action: We encourage the EMA to review and update this section and to include references to industry standard platforms (such as LHASA Mirabilis; (see Burns, M. J.; Ott, M. A.; Teasdale, A.; Stalford, S. A.; Antonucci, V.; Baumann, J.-C.; Brown, R.; Covey-Crump, E. M.; Elder, D.; Elliott, E.; et al. New Semi-Automated Computer-Based System for Assessing the Purge of Mutagenic Impurities. Org. Process Res. Dev. 2019, 23 (11), 2470−2481 and refs therein)).	
409	6	The section on "front loading of control strategy…" is not helpful as written. All parties are aware that where work can be predicted, planned and completed earlier this will remove activities from the critical path and such planning reflects current practise across the industry. However, the general intent is not necessarily possible for rapid development for unmet medical need, especially where adaptive clinical programs change timelines, and/or where promising products are in-licensed from third parties. In addition, the concept of front loading development work to remove it from the critical path is not unique to the development of the control strategy. **Proposed change:** Consider the intended audience for this this section and either remove it or move and adapt it to use earlier in the Toolbox. Also consider how this can be aligned with situations where PRIME designation has not yet been obtained.	Accepted. The specific subsection has been deleted. An introduction to the section before 4.4.1 is being added to address general aspects of control strategy including front loading while realising such front loading may be difficult. It is recognized that expedited development programs have a number of challenges: e.g. limited manufacturing and clinical experience, , process and method validation studies not finalized, and understanding of criticality and interactions. Despite this, these products are still expected to be safe and efficacious with a positive benefit risk ratio. Flexibility in what CMC information will be required for marketing approval will depend on factors such as product and process knowledge, analytical capability and the quality system. Whenever possible it may be a good practice to frontload certain process development activities. This could include early planning of small-scale studies required to

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			establish process parameter ranges and conducting risk assessment activities to identify and mitigate gaps in process development and evaluation
416-440	5	The section on using product from sites used to manufacture investigational medicinal products remains unclear. Initially, it appears to suggest that product manufactured at a manufacturer that holds only an MIA(IMP), rather than a full MIA for commercial product, should be able to be released for initial commercial supply based on a risk assessment. This would make sense for PRIME products and other products for high unmet medical need, while technology transfer to a manufacturer with a full MIA takes place or while the MIA(IMP) holder applies for a full MIA. However, this paragraph then seems to state that in fact a full MIA will need to be granted before a positive Opinion on the MA can be granted. This makes the whole paragraph unclear as to what is being proposed and what the flexibilities indeed are. If it just means that batches manufactured at the MIA(IMP) holder prior to the granting of a full MIA (for commercial product) may be able to be released to the market post approval of the marketing authorisation, but only once a full MIA has been granted or manufacturing transferred to a full MIA holder, then this needs to be made clearer in this paragraph. **Proposed change:** At line 431 – "…MIA has been granted. However, in some cases it may be acceptable for initial commercial, marketed batches of the product to have been manufactured at the MIA(IMP) holder's site before granting of a full MIA for commercial product. In such circumstances, evidence that an adequate level of compliance to GMP …"	Not accepted. Currently this is a EU legal requirement, and cannot be overruled by a guidance document.

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416	6	Overall, the section on GMP does not address some of the key considerations of the workshop. For example, the toolkit section on GMP inspections should clarify that for commercial supply of early access medicines for unmet medical need, considerations related to GMP manufacture during the clinical phase might be considered acceptable/normal to inspectors (e.g. greater variability in product yield, more frequent changes/interventions to process conditions, more frequent validation exercises…). This section should also make reference to concepts discussed at the workshop related to the need to strengthen scientific advice/agreement between regulators on GMP matters.	Partially accepted. The text has been revised as follows: In such circumstances, although the limited manufacturing experience can be taken into account, evidence that an adequate level of compliance to GMP to manufacture marketed products is in place, that an effective Pharmaceutical Quality System. As indicated above, scientific advice can be requested in any area. This is a stand-alone process, and is not to be described in detail in this overarching guideline.
416	6	In the section on GMP, industry is disappointed with the section on launching from an investigational medicinal product site. In the 2018 workshop, it was universally considered appropriate that GMP material produced from an IMP site without a commercial license is appropriate for early patient access. The expectation in the toolkit that a commercial licence (MIA) must be obtained prior to a CHMP opinion seems linked to inflexible regulations and is not aligned with the recommendations from the workshop. This point is also not aligned with the principles on "decoupled validation" (line 314).	Not accepted. Currently this is a EU legal requirement, and cannot be overruled by a guidance document. A commercial license has to be obtained and that can also be obtained by a IMP site. Some flexibility can be applied with respect to the process (see previous comment).

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			Decoupled process validation can (only) be performed in a site that is licensed (but process validation activities can start before or after obtaining the GMP licence).
416	9	Clarification should be provided as to the applicability of launching from an investigational medicinal product site for ATMPs given that the specific ATMP GMP guideline allows for additional considerations and adaptations for investigational products on topics such as qualification and validation, possible use of wider specifications etc. as well as the possibility to manufacture the product in an open system in a critical clean area of grade A with a background clean area of grade C	Not accepted. Currently this is a EU legal requirement, and cannot be overruled by a guidance document.
426-427	6	Regarding this specific point:" *A commercial manufacturing authorisation issued under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to manufacture marketed products will be required at the time of the Opinion of the MA. Therefore, the applicant should ensure that the necessary application for the relevant MIA is submitted to the relevant supervisory authority in time to allow inspection prior to the grant the Opinion*" Clinical trial supplies are manufactured to EU GMP hence the risk to product quality is low. While its recognized that an MIA would be required for open-ended supply from a clinical site, a distinction should be made in cases where a limited number of batches will be provided to facilitate earlier launch while commercial operations come on stream. We note the text in the 2018 PRIME Quality workshop report (p15):	Not accepted In line, with current EU legislation a commercial manufacturing authorisation issued under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to manufacture commercial products will be required at the time of the Opinion to the MAA. As described above, and in the guideline, in certain cases, to facilitate timely patient access to medicines that address unmet medical needs certain flexibility and acceleration of the licensing procedure can be considered. See further comments above.

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		"*Development sites supplying clinical studies are well suited to rapid scale-up and manufacture. They are used to rapid turnover of products and processes to support multiple clinical programs and are used to running processes where knowledge is more limited and where unforeseen events and deviations can occur more frequently. Companies use this as part of building process knowledge during development*" And the subsequent recommendation: We strongly urge the EU to work to enable IMP GMP manufacturing sites to be used to supply commercial materials (where agreed, and for the conditions and timescale agreed) via updates as required to Article 40 or other measures such as the allowance of temporary derogations.	
436	6	Please clarify this sentence: "*The use of a Comparability Assessment exercise (See 4.6) could be considered and applied for the evaluation of GMP gaps to support the certification and release of the marketed batches*." We note the reference (4.6) is to stability. We also note the EMA 2018 PRIME Quality workshop report refers on p16 to a "*GMP comparability plan and gap analysis*" and p17 "*Using comparability as the basis for accepting clinical trial data which has been generated with product manufactured in a facility not fully compliant with GMP requirements* " which seem to be in a different context to this section.	Partially accepted Proposed change: The use of a comparability assessment exercise (See 4.7) could be considered and applied for the evaluation of GMP gaps.
441 – 445	2	We request that should there be a GMP inspection, it should be clarified whether these inspections are done on an announced or a spontaneous basis	Not accepted. This is not specific to PRIME, or early access. Please refer to general guidance available about the GMP inspection.

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443-445:	6	The text can benefit from being more specific **Proposed change:** "*Submission of the ~~supply chain information~~ on the manufacturing and distribution sites in advance of the submission is necessary to evaluate, the need for a GMP inspection and to co-ordinate any requested inspection within the assessment procedure.*"	Partly accepted. Proposed change: Submission of the ~~supply chain~~ information on the sites responsible of manufacturing, testing, EU batch release and distribution ……
446-448	6	It could be helpful to provide clarification on what is meant by "*appropriate mechanisms to share knowledge and information obtained through inspection or assessment activities…*". For example, are "mutual recognition" GMP inspections and "virtual" GMP inspections considered as options to facilitate a review of GMP compliance and thus help prevent delays?	Partially accepted The text will be updated as follows: During accelerated timelines, it is important to ensure that the timing of quality review and GMP inspection activities are aligned, and appropriate mechanisms to share knowledge and information obtained through inspection or assessment activities are utilised by the EMA to facilitate the evaluation of a MAA and vice versa. The modalities to conduct GMP inspections is out of the scope of this guidance.
449	6	GMP does not apply before the API starting material. In addition, the ICH Q7 Q&A i.e. CHMP/ICH/468939/2015, 1. February 2016, Q&A No 1.1. states that an '*appropriate level of controls suitable for the production*' should be applied **Proposed change:**	Accepted. Proposed change: Use of biological starting material manufactured under an ~~lower~~ appropriate level of GMP an

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Use of biological starting material manufactured under ~~a lower level of GMP~~ an appropriate level of controls suitable for the production	appropriate level of controls suitable for the production
452-454	9	The sentence "the level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principle should always be adhered to" approach potentially misleading. It is our understanding that full GMP should be applied from early clinical development forward for small molecules and biologics. Only ATMP are allowed certain level of flexibility as per Part IV GMP for ATMPs. **Proposed change:** "For small molecule and biotech full GMP is expected for the manufacture of active substance and drug product from early clinical development forward. For ATMP, the level of GMP increases in detail from early to later steps in the manufacture of the Drug Substance and Drug Product, ~~active substances~~ but GMP principle should always be adhered to"	Partially accepted. Text revised as follows: The level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principles should always be adhered to. Under exceptional conditions, it could be acceptable to use active substance starting material (e.g. a MCB developed in an academic setting) that may be considered by the applicant to have been manufactured under ~~a lower~~ an appropriate level of GMP. This requires that~~, provided~~ documentation is available to confirm traceability, and prevention of contamination, including information related to components used during development with potential impact on product safety, and that an extensive characterisation and testing have been carried out using appropriately qualified assays and according to the approved control strategy. A documented risk assessment should be conducted to identify the testing requirements and/or other measures necessary to ensure the quality of the starting material and the medicinal

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			product. Sufficient documentation should be available on the production of the starting material. ~~and also~~ A comprehensive viral safety study complying to GMP should also be performed, where relevant. The competent authorities will evaluate the risk assessment and should agree to the proposed strategy in the context of the assessment of the marketing authorisation application/clinical trial authorisation application.
453	8	"*Under exceptional conditions, it could be acceptable to use starting material (e.g. MCB) that may be considered by the applicant to have been manufactured under a lower level of GMP,…*" If material using a lower level of GMP is acceptable, another question that would arise is around the status of the analytical assays that are supporting the activity. Would these need to be qualified, characterized or fully validated methods? Could the Agency clarify?	Partly accepted Proposed change: Under exceptional conditions, it could be acceptable to use active substance starting material (e.g. a MCB developed in an academic setting) that may be considered by the applicant to have been manufactured under ~~a lower~~ an appropriate level of GMP. This requires that~~,~~ ~~provided~~ documentation is available to confirm traceability, and prevention of contamination, including information related to components used during development with potential impact on product safety, and that an extensive

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			characterisation and testing have been carried out using appropriately qualified assays and according to the approved control strategy.
454	8	"*Under exceptional conditions, it could be acceptable to use starting material (e.g. MCB) that may be considered by the applicant to have been manufactured under a lower level of GMP,…*" What data would be expected from the Regulators should the starting materials be moved to GMP production? Would there be an expectation that a comparability analysis is required prior to introduction of the GMP starting material? Also could clarity be provided on expectations for establishment of shelf life of non-GMP starting materials?	Not accepted The materials are not expected to be replaced when moving to GMP. The same MCB is to be used. Therefore, comparability is not an issue. Shelf-life demonstration expectations are no different for these materials.
454	5	*"Under exceptional conditions, it could be acceptable to use starting material (e.g., MCB) that may be considered by the applicant to have been manufactured under a lower level of GMP,…"* If material using a lower level of GMP is acceptable, another question that would arise is around the status of the analytical assays that are supporting the activity. Could the Agency clarify - would these need to be qualified, characterized or fully validated methods? Also, what data would be expected from the Regulators should the starting materials be moved to GMP production? Would there be an expectation that a comparability analysis is required prior to introduction of the GMP starting material. Finally, could clarity be provided on expectations for the establishment of shelf life of non GMP starting materials. A clarification on the meaning of "lower level of GMP" for starting biological materials would be helpful.	Partially accepted. Changed from 'lower level' to 'appropriate level of GMP'. Furthermore, see response to the previous two comments.

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454-458	9	It is stated that it could be considered acceptable to use starting material (e.g. MCB) manufactured under lower level of GMP provided documentation is available to confirm traceability and prevention of contamination, etc In order to capture ATMPs it should be clarified whether lower level of GMP would also be applicable to starting material used for the manufacturing of ATMP in line with the EMA Q&A guidance of 23 April 2021 addressing how good manufacturing practices (GMP) principles should be applied to starting materials for advanced therapy medicinal products (ATMPs) of biological origin. EMA said that the Q&A is not meant to set new GMP requirements but rather to give guidance on "what principles of GMP mean and how to implement them." The guideline describes "minimal" requirements in the fields of quality management, risk management and production and quality control applicable to relevant starting materials. The guidance states that "a GMP certificate is not required for manufacturing and testing sites of starting materials for ATMPS. For certain starting materials of biological origin (such as e.g., linear DNA used as template for ex vivo transcription into mRNA, plasmids to generate viral vectors and/or mRNA, and vectors) used to transfer genetic material for the manufacturing of ATMPs it is, however, mandatory that the principles of GMP are complied with."	Not accepted. That is a different situation. The text has been modified to explicitly mention a MCB developed in an academic setting. This is a clear exceptional situation. The principles of GMP as explained in the Q&A are not specific for Accelerated Access (PRIME) and are not included in the toolbox guidance.
455	6	To be clear in the terminology as 'starting material' is defined to be an API or excipient in the EU legislation **Proposed change:** API starting material (e.g. MCB)	Accepted. Proposed change: active substance starting material (e.g. MCB)

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456-464	5	Suggest that a common consideration currently is the plasmid used for the production of vectors which are subsequently used to genetically modify cells for a cell-based ATMP. An example of the specific considerations and types of information that would help to understand the quality and consistency of the plasmid starting material would be valuable. Ideally consistent with the current FDA thoughts on plasmid quality in this context. **Proposed change:** For example, add: "Plasmid starting materials used for vector manufacture where the vector is then used to produce cell-based ATMP are a particular example. To support the use of plasmids, information in the dossier should include specific measure to assure quality e.g., confirmation of plasmid manufacture under a quality management system and plasmid cell bank testing as per Ph Eur 5.14., consistent with the principles outlined in the EMA's Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs"	Not accepted. The use of starting materials manufactured under the principles of GMP is not what this section is referring to. We refer here to e.g., cell banks developed in academic settings. That is different from plasmids for vector manufacturing .
458-460	5	The following statement is made "A documented risk assessment should be conducted to identify the testing requirements necessary to ensure the quality of the starting material and the medicinal product." For some risks, it may not be possible to mitigate these risks using testing i.e., to ensure the quality of the starting material and medicinal product e.g., potential exposure to TSEs.	Accepted. Proposed change: A documented risk assessment should be conducted to identify the testing requirements and/or other measures necessary to ensure the quality of the starting material and the medicinal product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "A documented risk assessment should be conducted to identify the testing requirements and/or other measures necessary to ensure the quality of the starting material and the medicinal product."	
460	6	The qualifier 'sufficient' is not needed and can raise concerns. Either the manufacturing is documented or not. **Proposed change:** ~~Sufficient~~ documentation	Not accepted. Poor documentation is still documentation, but not sufficient.
465	9	Scientific tools for stability provide specific guidance for biotech products and small molecule. Guidance related to Stability of ATMPS composed of cells should be provided since stability studies are often limited by the availability of materials and specific storage conditions.	Not accepted. Stability guidance on specific types of products is beyond the scope of this toolbox. It will be considered in the remit of stability guidance documents.
466	6	The section on stability is welcome, but would benefit on a further discussion in the introductory paragraph of science and risk based approaches to stability applicable to all product types. Given stability is usually on the critical path for development, there should be discussion of the use of complimentary approaches to the rigid interpretation of ICHQ1 and Q5C, and in guidance for development, registration activities and post approval changes (e.g. reduced studies where justified on the basis of utilisation of prior knowledge, use of extrapolation and/or kinetic data modelling and science and risk-based approaches to the definition of what is a "representative" batch). The approaches based on prior knowledge and risk assessment, using modern approaches such as a general assessment of product stability, extrapolation and	Partly accepted. The introduction is being extended. Updated text for the introduction to section 4.6: In accelerated development programs, standard stability data packages may not be feasible and alternative ~~paths~~ approaches ~~may be needed while still assuring~~ used to demonstrate the stability of the product. Based on scientific justification, which may include prior knowledge and/or data from development/pilot scale batches of the same formulation, it may be possible to submit less

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		modelling described in the subsequent sections are general, and likely to be reflected in future updates to ICHQ1 and 5c. Also missing is the general principle that real time data can be obtained earlier (e.g. from set down of clinical batches), if there is a scientific justification that subsequent changes to the product or process have not impacted the stability. This could come from comparison of the quality of the product or supporting data from stress conditions, or modelling.	data than described in ICH guidelines. Data may cover shorter times (e.g. 6 months) than those recommended in available guidelines. In some cases, where a consistent stability pattern is seen, it may be acceptable to include data from less than 3 batches. Data from clinical batches may be used to support the shelf life, but any subsequent changes to the product or process should be explained, and it should be considered whether these changes could impact product stability. Applicants are encouraged to initiate dialogue with EMA to discuss their use of alternative stability approaches to ensure there is a mutual agreement on the dossier expectations.
466-467	5	Suggest to clarify the expectations and considerations for the use of stability data where the analytical methods used are not consistent with the final proposed release specification and/or subsequent method changes are planned/made. Also, with respect to the performance of the methods used where these have not been validated. Also suggest to highlight the concept of "primary" and "supporting" stability batches and how these can be defined and used e.g., via the principles of the ICH stability guidelines.	Comment noted, but since the aspects with changes to analytical methods during stability studies and what is considered primary and supporting data do not differ from standard applications, no further text is added.
468-506	5	Stability for biotech products. It would be very useful if ATMPs could specifically be mentioned here. For example, many ATMPs are cryopreserved and stored at ultra-low temperatures. Prior knowledge of other cell based products that are formulated	Accepted. See below.

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		in the same cryopreservation solution (excipient) and using the same cryopreservation process could potentially support the shelf-life of a similar product if similar trends are observed over short to medium term testing. This is particularly useful for cryopreserved ATMPs where accelerated stability testing is not feasible. In our opinion, whilst not being applicable to ATMPs in the present draft, the section on Stability models generated from stability of structurally similar molecules (Biotech) is the clearest on what flexibilities can be used and how they need to be communicated, with several key examples of what is and is not acceptable (e.g., vial versus syringe). We would advocate for a similar approach in other sections as well.	
468-469	6	It would be important to ensure that applicability to all Biologics (e.g., including Vaccines) could be considered. To this aim, it is suggested to change the title. **Proposed change:** "Use of stability models for biological therapies and vaccines ~~Stability models generated from stability of structurally similar molecules (Biotech)"~~	Accepted. Initial wording of the title is too limited and therefore changed to spell out applicability for biologicals in general while indicating that the applicability will differ with complexity of the product. **Title: Stability models generated from stability of structurally similar molecules (Biologicals)** **…** *To Insert after line 502:* The approach to use (models based on) prior knowledge to extend the claimed shelf-life can in

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			principle be applied to all types of biologicals (including e.g., mAbs and other therapeutic proteins, vaccines, viral vectors, cell therapy products). However, it is acknowledged that the principles will be difficult to apply to other groups of products and formulations than those used to establish the model (i.e. a model based on mAbs is unlikely to apply in general to other types of recombinant products). ~~The generation of a predictive stability model and its 505 application should be agreed in advance with the agency.~~ Especially for complex products, the prior knowledge is expected to be based on very similar products (e.g. same viral vector with a similar genetic construct carrying a different gene of similar size).
468	8	In our opinion, this section is the clearest on what flexibilities can be used and how they need to be communicated, with several key examples of what is and is not acceptable (e.g. vial versus syringe). We would advocate for a similar approach in other sections as well.	Comment noted. Guidance has been provided in other sections, as relevant.
468-506 Specifically,	8	In general, we appreciate the proposed approach on stability data, and if a molecule is well-behaved based on stress stability data, this technique works well. However, in the protein space, these models can be difficult.	Partially accepted. Proposal for rewording lines 468-469 see above.

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line 472		Therefore, we are wondering with the wording in line 472 "*...could be extrapolated using predictive stability models generated from prior knowledge of the stability of structurally similar molecules.*" Could the Agency also clarify what are acceptable approaches to address accelerated/stress conditions for stability studies for *cryopreserved cellular product*. Cellular products have very limited stability/shelf life outside very defined temperature ranges. Further, this section does not consider specific products such as ATMPs and mAbs or link back to platform formulations/prior knowledge and the stability of cells/viral vectors in general at low temperatures. For storage at -70 for viral vectors, nucleic acids, and for cells at -150C lack of discernible degradation profiles and degradants is a property that's well understood and leveraged for e.g. Master/working cell banks which can be stored under a stability protocol in liquid nitrogen for years and decades as it's been established that there is little effect to the critical parameters of the cells. Similar principles could be applied to ATMPs. **Proposed change:** Update this section to also include applicability of concepts to specific products such as ATMPs and Abs as appropriate. Insert after line 502 and before line 503	The current text already emphasises the need to justify the fit of the model to the molecule/ product in question. Specified recommendations for documentation to be submitted for mAbs and ATMPs are beyond the scope of this overarching toolbox guidance.
471, 472, 486,	6	As previously highlighted, to fully facilitate the availability of medicines addressing unmet medical need then the tools highlighted should be applicable to products which are eligible for Early Access Approaches in general and not specifically PRIME	Accepted. Point taken. Text has been revised to make clearer that this document could also be applied on a case by case basis, prior to agreement with EMA, for certain non-PRIME

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		products. Stability is one of the areas where a more general application of new tools is considered highly appropriate. However, in contrast to other sections of the Guideline (e.g. Process validation) the section on stability models for biological products uses the term PRIME products almost exclusively. **Proposed change:** Replace "PRIME Products" throughout with "products in early access approaches".	products which also address an unmet medical need.
472-474	6	The section outlines the use of prior stability knowledge etc model the stability profile for 'like-molecules'. The guidance is allowing for extrapolation of the product-specific stability knowledge. Therefore, other approaches should also be considered that have developed for biologic product application since the 2018 stakeholder workshop such as 'Advanced Kinetic Analysis' that empirically fits the stability data obtained at recommended and accelerated storage conditions to increasingly complex kinetic equations. This approach has been used to support the stability information of some vaccines. Other kinetic extrapolation approaches are also being developed that may also be combined with prior knowledge and leveraging Artificial Intelligence to accurately predict the stability of complex biologic products. Consistent with prior comments, consider that there is no specific scientific or technical reason why the science and risk-based tools for stability described in this guidance could/should not be applicable to medicines progressed under any accelerated access scheme rather than restricted to PRIME. **Proposed change:** For ~~a biologic PRIME~~ an early access biologic product, trends in stability data, and therefore the claimed shelf life, could be extrapolated using	Not accepted. It acknowledged that other opportunities exist like the advanced kinetic analyses but these have not been applied for and experience is thus lacking. At the current stage it is therefore premature to include them in a guidance document. This may come in a later revision. Companies may still use these approaches but are recommended to discuss this with the relevant regulatory agencies before submission.

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		predictive stability models generated from prior knowledge of the stability of structurally similar molecules, or from appropriate kinetic models. In such cases ….” (The rest of the paragraph is suitable for other stability models).	
479 - 480	6	The text is specific to the use of prior knowledge from like-molecules. Edit needed to accommodate other modelling approaches. **Proposed change:** “…. Provided in the dossier. When using stability prior knowledge from related molecules to generate a stability model, the types of products from which the model was derived should be described.”	Not accepted. The model is based on prior knowledge and building a model from this. The proposed addition “When using stability prior knowledge from related molecules to generate a stability model” therefore makes no sense.
479-483	5	Suggest to clarify how much detail might be expected for other products and considerations if access to this information is limited e.g., the applicant does not have oversight of these products and cannot assure data integrity.	Comment noted. The expected level of detail will be a case by case situation and it is not possible to describe this in the toolbox guidance. The applicant should justify the model proposed with sufficient background data, be it internal information or a mix of internal and external documentation. The model can only be accepted in case sufficient data is available.
481	9	Suggest replacing “Company” with “Applicant” or “developer” throughout the document, as appropriate **Proposed change:** “the Applicant should provide a rationale for […]”	Comment noted. Nomenclature aligned.
483	6	Stressed stability conditions frequently change the mechanism of degradation, as well as the kinetics, and can be artificial. Therefore, stressed conditions may	Accepted.

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		mechanistically not be wholly representative of the product degradation pathway under the recommended storage condition. Accelerated conditions are expected to better represent the mechanism of product degradation under normal handling. **Proposed change:** "Data from accelerated or stress studies could be submitted to further support the shelf life"	
489	5	Suggest this reads as if the release criteria are set based on the required shelf-life. Propose to clarify how the stability study (and release) acceptance criteria would/could be set based on the accumulated understanding of the stability profile (trend).	Accepted. Proposed wording "In cases where the data for the new product fits the model, while considering the change over the proposed shelf life, ~~it should be possible to set~~ more stringent release acceptance criteria should be set which would assure that the clinically relevant quality attribute limits are met at the end of shelf life ~~should be set~~"
495-496	8	*"There are situations where the models do not fit. It is important to find out why and apply this knowledge to new products in order to decide early on if the model would fit or not"* **Proposed change**: an additional case where there is no change over time, but limited/variable data cause wide CI in prediction. Guidance on how to define zero slope would be appreciated.	Not accepted. The comment is outside of the scope of this toolbox guidance. Applicants are responsible of making and justifying the statistical analysis.
501	6	**Proposed change:** There should be no major changes (relevant to product stability) ~~to the production~~ apart from the container closure system.	Partially accepted.

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503-506	5	Suggest to clarify if this might be feasible for products such as viral and non-viral vectors and/or cell-based ATMPs. For example, for gene therapy products where the difference(s) between products is the transgene(s) and perhaps also the promoter.	Accepted. Wording has been changed in the title to include biologicals in general. Text has been added to point out ATMP specifics.
503 - 505	6	It is agreed that the approach described only applies when suitable prior knowledge is available to the Applicant. However, as discussed above, there are other, more recent, approaches being investigated that do not rely on prior knowledge and should be included in the guideline. This includes 'Advanced Kinetic Modelling'. Overall, lines 479 to 502 are applicable to any stability modelling approach. **Proposed change:** "…. unlikely to apply in general to other types of recombinant products). In this case the use of suitable kinetic modelling at the recommended and accelerated storage conditions may be justified. The generation of predictive …."	Not accepted at this stage. See above.
508-510	6	The principle of using prior knowledge from similar molecules or products to support the stability assessment of the API/product in scope is welcome. It is also useful that stability data from the same molecule could justifiably be used (e.g. from other commercial formulations or used in clinical batches where the changes made have been justified to not impact the quality and stability of the product or API. Long term data from such products may be available even beyond the minimum required 12 months at long-term storage conditions).	Comment accepted.

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		Proposed change: "*It is acknowledged that in some cases general prior knowledge of the stability of an active substance can be gained from similar molecules e.g. within the same class, considerations of functional groups in the molecule and the relevant environment regarding e.g. pH and moisture. Prior knowledge may also be available on the stability of products containing similar molecules or utilising prior knowledge of molecular stability from other formulations of the same molecule. Knowledge can also be gained from the use of accelerated stability using more challenging conditions of temperature and humidity, and modelling of the results…*"	
523 - 524	6	That 'regular' ICH stability studies are run in parallel would be more applicable to biologics than small molecules. For both prior knowledge and kinetic modelling approaches, the 'regular' stability study continuously verifies the model that is being used. For the relatively less complex and chemically more understood small molecules the confidence in ASAP and other stability models is sufficient to not require parallel long-term stability studies. The second part of the sentence seems redundant when commitments for biologic and small molecule stability have been outlined. **Proposed change:** Move first part of sentence to section 4.6.1: "~~Regardless of the approach taken,~~ Regular ICH studies should be ~~run in parallel~~ included to support the model and to continuously verify the model post-approval ~~and additional stability commitments provided, as described in ICH Q1A~~."	Comment not accepted. Long term studies are to be generated in parallel to confirm the adequacy of the model. Such data are not on the critical path regarding timing. This topic may be discussed as part of ICH Q1 revision.

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528	6	Comparability during (accelerated) development is primarily aimed at demonstrating that product characteristics are comparable across different clinical phases, while process understanding may still be evolving. Proposed addition (after line 561): Where prior knowledge is limited and/ or in the absence of statistically based acceptance criteria, it is appropriate to consider an approach aimed at demonstrating the preservation of quality attributes without the requirement of process consistency (in line with ICH Q5E). Therefore, comparability should be risk-based and phase-appropriate. The interconnectivity of CMC elements should be recognised and consistent throughout the guidance and thereby support a more holistic approach to product development. Limited manufacturing experience has multiple impacts across the CMC elements and approaches for one element (e.g. process validation) needs to be consistent with the other elements e.g. comparability, stability etc.	Point noted and relevant for early development. These recommendations are for the situations when clinical studies have been performed/completed and comparability has to be demonstrated, not just interconnectivity of CMC. The text is being revised as follows: A risk-based approach, such as the one developed for ATMPs, can potentially be used to tailor the comparability study ~~by identifying CQAs most likely to be impacted by manufacturing changes~~. This will allow, for example, a reduced comparability package focusing only on the relevant CQAs (4.7.2) or the use of prior knowledge (4.7.1). Based on this, a justified set of release, (accelerated) stability and/or ~~characterization~~ characterisation data can be used to demonstrate comparability. …. It is recognised that the level of comparability that needs to be demonstrated is dependent on the development phase. However, the recommendations given in this section are intended for later development stages in which clinical studies are ongoing or have been

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			performed and a full comparability exercise is required. Differences that are the result of enhancements of the process leading improvements in quality (e.g., improved purity profile) are generally acceptable.
528	6	4.7. Scientific tools related to comparability (biologicals) **Proposed change:** "Scientific tools related to comparability ~~(biologicals)~~. " Consider adding comparability concepts suitable for chemical entities and all modalities.	Point noted. As only biologicals were discussed during the workshop and there is little experience in this respect on complex chemicals it is premature to include them as part of this revision. This may be reconsidered in future updates. A footnote has been added as follows: *The guidance below on comparability strategy is intended for biologicals, although it is acknowledged that several elements could potentially be applied for other product types. If developers intent to use such a strategy to other products it is recommended to seek advice from the competent authorities.*
528-533	6	Section should discuss flexibility around the number of lots initially provided to allow implementation of a change. Similar to flexibility for process validation, use of an approach where a comparability protocol is submitted which allows implementation of a change based on assessment of a reduced number of lots. A more complete dataset is then submitted once the data becomes available.	Comment accepted and wording to be introduced..

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		Furthermore, different process validation approaches (section 4.3) may result in less than 3 PPQ runs prior to submission. **Proposed change** to add following line 532: "…. Can be used to demonstrate comparability. A risk-based approach to the number of lots used for comparability studies could be justified. For example, the number of PPQ lots used in comparability could follow the strategy for PPQ lot manufacture (Section 4.3) or additional representative lots may be justified."	
528-561	6	The discussions' use of prior knowledge to inform CQAs (4.7.1) and risk-based selection of CQAs (4.7.2) is not a novel concept and is not unique to PRIME scenarios. It is not clear why this is included in this draft Guideline **Proposed change:** Consider removing the content related to risk-based selection of CQAs and/or explaining when and how this flexibility would be uniquely applicable to PRIME scenarios.	Not accepted. As prior knowledge is the key enabler for accelerated access this should stay even if use of prior knowledge is not unique to PRIME processes.
529	8	ATMPs are specifically called out to benefit from risk based approaches for process validation studies. While a risk based approach can be leveraged for initial marketing authorisation application, post approval changes appear to not fall under the same category. It is appreciated that the PRIME toolbox is singularly focused on licensure but it should be made clear that a full comparability package will nevertheless be expected in the post approval space. Alternatively, a clear delineation should be provided when a risk based approach is considered acceptable.	Not accepted. It is expected that companies following approval of PRIME products gather the missing information. The post licensing part would not be that different compared to standard products and therefore it is out of the scope of this guidance to provide such level of detail.

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		Proposed change: Line 529- Instead of footnoting, provide additional detail on how this approach is continued post-approval to provide more clarity on how this tool plays out in life cycle management.	
535	5	Suggest to clarify what is meant and understood by a platform i.e., how the term may be defined. Where the same materials and manufacturing procedures (and facility) are used but there may be differences in the material characteristics of the inputs and/or outputs for each step e.g., due to differences in cell growth profiles between product starting materials – what might be the considerations for supporting the process as a platform and interpreting the platform data? Propose that further clarification would be highly valuable.	Not accepted. The platform is sufficiently defined in 4.2.1. Reference is made in the text to 4.2.1: " Prior knowledge (see 4.2.1) based on e.g. the same platform or from similar products can be used to predict the impact of specific manufacturing changes."
536-538	9	The sentence on risk based approach in the chapter focusing on prior knowledge appear redundant to what is later discussed in section 4.7.2 "risk based identification of the CQAs". **Proposed change:** to avoid redundancies, remove the sentence "A risk-based approach could potentially be applied to tailor… comparability data" since the topic is addressed in 4.7.2	Accepted. For better reading former sections 4.7.1 and 4.7.2 are put in reverse order. The redundant text is deleted.
541	5	"After the initial comparability studies an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies, before the final comparability exercise can be submitted." Could the Agency clarify which additional studies should be considered in the analysis?	Point noted: To cover the comment the following will be introduced: After the initial comparability studies, an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies.

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			Firstly, it should be considered if additional chemical-physical, immunological or other data are needed. If required due to non-comparable results that can have impact on the relevance of the safety and/or efficacy data gathered so far, the comparability exercise should proceed with the generation and evaluation of comparability non-clinical and/or clinical data as necessary to contribute to the conclusion of comparability of the product (see 4.7.7).
541-543	9	The sentence "After the initial comparability studies an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies, before the final comparability exercise can be submitted." Should be moved to the introduction This is indeed an important consideration as it brings the notion of tiered approach for comparability, first relying on the possibility to use a reduced approach supported by prior knowledge AND risk based approach, then completing with a final comparability exercise. This important concept is currently captured in the specific chapter focusing *on prior knowledge* and since it englobes the use of prior knowledge as well as risk based approach for initial CQA determination, we encourage to move the sentence as part of the introduction starting line 529 so that the tiered approach is presented as part of the global strategy capitalizing on both prior knowledge and RBA, rather than presented as part of the prior knowledge chapter:	Comment noted. Please refer to the answer above.

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		Line 529 "A risk-based approach, such as the one developed for ATMPs[4], can potentially be used to tailor the comparability study by identifying CQAs impacted by manufacturing changes. In addition, prior knowledge can also be used to support the design of initial comparability studies. This will allow ~~for a~~ the possibility to develop a tiered approach to comparability with an initial reduced comparability package focusing only on the relevant CQAs. Based on this, a justified set of release, (accelerated) stability and/or characterization data can be used to demonstrate initial comparability. After the initial comparability studies, an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies, before the final comparability exercise can be submitted"	
541-543	8	*"After the initial comparability studies an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies, before the final comparability exercise can be submitted."* Could the Agency specify what kind of additional studies may be needed? Non-clinical? Clinical?	Comment noted. Please refer to the answer above.
549-550	5	Suggest this is consistent with the principles of ICH Q5E which states "When considering the comparability of products, the manufacturer should evaluate, for example: • Relevant physicochemical and biological characterisation data regarding quality attributes;…". Propose to acknowledge this.	Not accepted This is contradictory to the intention to concentrate on CQAs, the proposed text doesn´t make a difference between critical and non-critical.

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559-561	5	Suggest to also clarify that in certain circumstances suitable analytical methods might not be available to assess the quality attribute(s) identified as potentially impacted. And, in this scenario that consideration should be given to the feasibility of developing a method or using other data such as from a non-clinical study (if possible) to address this gap.	Not accepted If appropriate development studies have been done the relevant (characterisation) assays for CQAs should be already available. If it is not possible to assign non-criticality to a QA, it should be included in the comparability studies.
562	5	There needs to be some guidance on the number of lots required to support changes. Not all changes require at least three lots (at scale) for a sufficient comparability assessment. Whilst the toolbox mentions the utility of small scale data, it would be helpful to be more direct in how that can act as a substitute for at-scale data. Could the Agency provide guidance on the number of lots needed to support change, and more guidance on utility of small-scale data as a substitute for at-scale data?	Not accepted. This will be a case by case situation and therefore not possible to specify the number of batches that may be required in all scenarios. The number of batches is dependent on the data.If these are not consistent, more batches will be needed. If good consistency is shown fewer batches can be accepted..
580	8	We strongly feel that there needs to be some guidance on the number of lots required to support changes. Not all changes require at least three lots (at scale) for a sufficient comparability assessment. While the toolbox mentions the utility of small-scale data, it would be helpful to be more direct in how that can act as a substitute for at-scale data. Further on, line 605 *"representative material".* To pursue small scale data with representative material, what level of detail would need to be filed to support the representative nature of the small scale batch?	Not accepted. Same comment as the one above. This will be a case by case situation and therefore not possible to specify the number of batches that may be required in all scenarios. The number of batches is dependent on the data. If these are not consistent, more batches will be needed. If good consistency is shown fewer batches can be accepted.

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		Could the Agency provide guidance on the number of lots needed to support change, and on the utility of small-scale data as a substitute for at-scale data.	The justification for the use of small scale data is also strongly dependent on the type of process. Therefore no general guidance can be given.
from line 580	4	Guidance acknowledges where may be cases of low batch numbers and therefore statistical tool may not be useful but neglects to offer suggestions of suitable alternative approaches. Some examples might be multi-variate analysis, t-test and/ or TOST.	Not accepted. Comment beyond the scope of this guidance document. The statistical tool to use would depend on the data set.
588	6	4.7.4 Statistical tools for comparability: Add detail to criteria of side-by-side analysis and further elaborate for product category where limited number of batches are available **Proposed change:** Inclusion of side-by-side analysis of individual values with accompanying descriptive statistics to summarize data (e.g. min-max and 3*sigma ranges, tolerance interval, equivalence) is recommended…	Not accepted. Tolerance interval and equivalence may not be very useful in case of very few batches.
594 - 595	6	It is not clear how the proposed comparison to historical data occurs in an accelerated program with few batches. Unless prior knowledge from 'like-molecules' are available, the historical data set is also likely to be highly limited with data too narrowly distributed to represent the variability of the product, process or assay. **Proposed change:** "…., in such cases a comparison with historic ranges may be the best approach in which pre and post-change data would be expected to fall within a range support by product attribute and assay knowledge."	Accepted. Knowledge of the assay and its variability is relevant. The text will be revised as follows: 'in such cases a comparison with historic ranges may be the best approach in which pre- and post-change data would be expected to fall within a range supported by product attribute and assay knowledge'.

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600	5	Could EMA clarify what are acceptable approaches to address accelerated/stress conditions for stability studies for cryopreserved cellular product? Cellular products have very limited stability/shelf life outside very defined temperature ranges.	Comment noted. The comment is valid. However, this is a general guidance and not meant to provide to provide product group specific stability study considerations.
607	5	"ATMPs in general are characterized by starting materials of inherent variability (for cell/tissue-based products), complex biological features and manufacturing processes. Therefore, ATMPs are outside the scope of the ICH Q5E guideline and a specific Q&A document is available: Comparability considerations for Advanced Therapy Medicinal Products (ATMP)- EMA/CAT/499821/2019. The Q&A document should be read in conjunction with this Toolbox document." We recommend further clarifying that the principles described in this section of the document do apply to ATMPs. We also would like to point out that for example AAV based gene therapies could follow the principles of ICH Q5E.	Accepted Text has been added to clarify this.
from line 613	4	The review group appreciates the inclusion of this section and would particularly welcome the opportunity for additional detail / examples of scenarios where additional nonclinical data might be needed to be added to bring clarity and aid practical application of the guidance.	Not accepted. These are case-by-case situations which should be discussed with the authorities. Examples where discussed at the workshop. The addition of examples may be considered in the future.
617	6	Overall, it might be beneficial to the flow of the document to move Section 5 to earlier in the document (eg. After Section 2 on scope, since many of the themes are closely linked to text in Section 1, introduction).	Not accepted. The regulatory tools are complementary to the scientific elements. Also, putting one or the other first is a matter of preference and wouldn't change the actual guidance provided.

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617	6	We note that all of the tools mentioned and Section 5 are applicable to non PRIME products and that there are no new PRIME specific tools or processes proposed.	As indicated in the text, this guidance has been developed to summarize in a single document the scientific elements and regulatory tools, available in the existing EU regulatory framework, so that it could serve as reference for applicants. MW To be revised in accordance with general discussion
617	6	Industry suggest that there should be reference to "rolling review" in this section.	Comment not accepted. 'Rolling review' is used exceptionally and not part of the EU regulatory framework.
617	6	Regarding the section on regulatory tools industry is disappointed that no reference is made to the following key points raised at the workshop • The need for ongoing close engagement and scientific advice in the post approval phase to support the many variations required. Industry notes that the PRIME program overall is focused on the clinical phase and initial approval, but that patient supply is equally important (especially in a pandemic scenario). • The need for meaningful scientific advice on GMP matters that will also consider reliance between member states and international partners with which the EMA has a MRA. Industry also requests clarification in how GMP SA advice is overseen by CHMP. • The need for clearer linkages on CMC matters between the PRIME/CAP and clinical programs in member states, to ensure discussion and decision on Quality matters are connect through clinical programs, the MAA and post approval.	Comment partially accepted. • The close engagement on the post approval phase will be emphasized. The scientific advice on GMP matters follows the same route as any other SA. The description of the SA procedure is out of the remit of this document, and stakeholders should refer to the dedicated guidance on the topic. • Quality is not seen in isolation but as part of the Q/S/E and overall Benefit/Risk evaluation. Please refer to EMA PRIME guidance: Enhanced early dialogue to facilitate accelerated

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		The need to enable less formalised scientific advice on CMC matters (e.g. no need to apply for a formal Scientific Advice, no full Briefing Book to be submitted, shorter timeframe to request and get advice ...)	assessment of PRIority Medicines (PRIME) - rev 1 (europa.eu). In case a PRIME applicant identifies a topic warranting further discussion, they can contact the EMA PRIME Scientific Coordinator who will advise on the suitable way to address the matter. Depending on the nature of the topic to be discussed, it can be discussed directly with the CHMP/CAT Rapporteurs and the EMA product team. For major/more complex issue, applicants may however be advised to seek scientific advice.
617-722	9	Section on regulatory tools would gain in clarity if slightly reshuffled and if a clear statement is made that these do not apply specifically to PRIME products with however stronger involvement and support from the EMA to these products. **Proposed change:** Suggest splitting the information into 1. Support during the development (incl. scientific advice) that would be moved from the introduction to a specific section; 2. Accelerated assessment and CMA; 3. Post approval tools	Comment noted. As indicated in the text, this guidance has been developed to summarize in a single document the scientific elements and regulatory tools, available in the existing EU regulatory framework, so that it could serve as reference for applicants. The second comment suggests generally the approach that has been followed. The inclusion of the suggested titles would result in inaccuracies as scientific advice can also be provided in the post-authorisation phase, and PAMCP can be included in the original MAA, not only post-approval.

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619-620	7	It is important to highlight that paediatric population is a population that require particular attention. **Proposed change:** EMA is committed to enabling early patient access to new medicines, particularly those that target an unmet medical need or are of major public health interest as the paediatric population	Not accepted. Comment is noted but considered out of scope of this guidance. The Agency is committed to support development of new medicines for use in the paediatric population, in particular in areas of unmet medical need including (but not being limited to) rare childhood diseases
625	8	A more flexible and iterative scientific dialogue is needed for complex global product development. A 40-day advice must be guaranteed for PRIME. Also, should continue to push EMA to clarify what development feedback the rapporteur can provide to companies outside of formal SA For expedited developments, or product under BTD, RMAT, RTOR, we should strive to clearer and shorter timelines from the point of meeting request to feedback. **Proposed change:** Add "A rapid advice procedure should be guaranteed for PRIME or BTD, RMAT, RTOR products (at max 40-day). Equally it is important to further clarify what feedback the assigned Rapporteur can provide outside of formal scientific advice" to Line 625	Comment noted. The definition of the scientific advice procedure and changes to it are out of the scope of this document. However, the comment will be considered in the context of the ongoing 5-year review of the PRIME scheme.
625	5	"a) scientific advice/protocol assistance during development, whereby the EMA provides medicine developers advice on the most appropriate way to generate robust evidence on a medicine's benefits and risks. This supports the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. Scientific advices are particularly suitable to agree with the EMA on tailored	Comment noted. The actual scientific advice procedure is out of the scope of this guidance document. However, the comment will be considered in the context of the ongoing 5-year review of the PRIME scheme.

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		development approaches such as filing with an initial more restricted control strategy, concurrent validation approaches, prior knowledge etc.". As indicated in our general comment on scientific advice, in our experience for PRIME products we found the scientific advice procedure to be quite inefficient, with long timelines from application to scheduling meetings and receiving final feedback endorsed by SAWP/CHMP. Expedited developments require clearer and abbreviated timelines from the point of meeting request to feedback (closer to e.g., FDA Type C meetings). PRIME designation should provide an advantage over current protocol assistance/scientific advice timelines and an implementation of a 40 day timeline is suggested. Equally it is important to further clarify what feedback the assigned Rapporteur can provide outside of formal scientific advice.	
631	5	What is meant by "consultative advice"? If this is a more informal and flexible way of approaching the two agencies for guidance it would be a welcome opportunity and more information would be appreciated. Expedited CMC developments need flexible approaches to seeking advice, and more opportunities to enable international alignment of requirements.	Please refer to general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf (europa.eu).
631	6	We note the sentence "*Applicants can also request a parallel scientific advice or a consultative advice with EMA and US FDA to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies in both regions"* which was also referred to in the 2018 Workshop. Industry is not aware of guidance on consultative advice on Quality (inc GMP) matters between FDA and EMA and request that further information is provided.	Please refer to general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf (europa.eu).

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631	8	"*Applicants can also request a parallel scientific advice or a consultative advice with EMA and US FDA to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies in both regions. The agencies conduct this procedure under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA. Further information can be found on the dedicated EMA website (references below*)." What is meant by "*consultative advice*"? If this is a more informal and flexible way of approaching the two agencies for guidance it would be a welcome opportunity and more information would be appreciated. Expedited CMC developments need flexible approaches to seeking advice, and more opportunities to enable international alignment of requirements.	Please refer to general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf (europa.eu).
645	7	The Agency seeks to support the medicine development process from an early stage. However, the Paediatric Regulation states that a Paediatric Investigational Plan should be granted in advance when a paediatric development is foreseen. **Proposed change**: needs as a Paediatric Investigation Plan at due time (early adults clinical) that will be granted by the PDCO detailing all quality, preclinical and clinical paediatric medicine development commitments. This plan should be aligned with the PRIME designation process and its content should be considered to support quality data packages for PRIME marketing authorisation applications.	Comment not accepted. The comment is outside of the scope of the guidance, which focuses on scientific elements and regulatory tools to support quality data packages. For guidance on general or PIP requirements refer to Paediatric investigation plans | European Medicines Agency (europa.eu)
654	6	In the section on accelerated assessment the document states: applicants should aim at filing a complete MA dossier and avoid the submission of data during the review, to avoid the timetable is reverted to normal due to major objections raised during the evaluation (e.g. major objections include concerns related to an	Comment not accepted. That paragraph was added to clarify the expectations and be clear that major objections would revert the timetable to normal. It is in the interest of applicants that

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		insufficient control strategy. Whilst this good practise, this seems out of place in a document intended to primarily address scenarios where this is not a plausible strategy and contradicts advice on later provision of data. It also highlights that the document is missing an important section on "rolling review".	this is clear so that this is taken into consideration when preparing the MAA dossier and avoid this scenario happens. Rolling review is not part of the EU regulatory framework.
659-665	5	We suggest that the current mis-alignment between accelerated assessment timelines for ATMPs (120+30 days) vs non-ATMPs (90+30+30 days) is revised and the ATMP timelines are aligned with the non ATMP timelines to provide the possibility of 2 rounds of questions.	Comment not accepted. The TT for accelerated reviews is not the scope of this document.
675	6	*'Conditional marketing authorisations should be restricted to situations where only the clinical part of the application dossier is less complete than normal'*. While it is recognised the legal basis for CMA does not support less than full pharmaceutical data with the exception of a public health emergency, this is not realistic, as CMC needs to keep pace with clinical development. Similar innovative regulatory approaches devised to facilitate accelerated, risk based clinical development are needed for CMC to deliver sustainable acceleration of products to patients. CMC development needs to be considered on a risk:benefit basis **Proposed change***: "Conditional marketing authorisations should be restricted to situations where only the clinical part of the application dossier is less complete than normal. CMC data and information will be reviewed on a benefit : risk basis applying approaches such as those within this toolbox."*	According the current EU regulatory framework for a conditional marketing authorisation, a less comprehensive quality dataset is only foreseen for medicinal product to be used in emergency situations.

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675-678	9	The proposed guidance is applicable to products that have PRIME and for which flexibility in terms of quality data at the time of MAA is introduced. However, this paragraph states that "CMA is restricted to situations where only the clinical part of the dossier is less completed than normal". This seems contradictory with the intent of the guidance itself… Could the Agency clarify if for PRIME products that are seeking CMA, the quality package could also be less comprehensive?	According the current EU regulatory framework for a conditional marketing authorisation, a less comprehensive quality dataset is only foreseen for medicinal product to be used in emergency situations. As indicated in the document 'Incomplete pre-clinical or pharmaceutical data should be accepted only in the case of a product to be used in emergency situations, in response to public health threats'.
688	9	As part of the presentation of regulatory tools such as PACMPs, and PAM, the ICH Q12 should also be discussed as it provides an opportunity to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. The concepts of life cycle management planning discussed within the ICHQ12 can also help developers of products under accelerated approval pathways anticipate and organize their post approval commitments and life cycle management activities.	Comment noted. This guidance document should not be read in isolation, but together with other applicable guidance. ICH Q12 is referenced in section 3.
695	6	We note this point: *"the protocol would describe the specific changes that a…"* A degree of flexibility is needed when scoping out changes for a PACMP as the precise changes may not be known until the data are reviewed from the studies proposed in the PACMP, for example manufacturing process parameters following a site change or scale up. It therefore may not always be possible to meet the proposed requirement to define 'specific changes'.	Not accepted. In order to agree on the protocol and the supportive data needed and downgrade the implementing variation it is necessary to know the changes the applicant intends to make. If changes are needed, it is possible to revise the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: *'the protocol would describe the ~~specific~~ changes that a…'*	PACMP post-approval or submit the change as a standard stand-alone type II variation.
702 PAMs	6	The company Pharmaceutical Quality System (PQS) is an additional regulatory tool which can be used to support the elaboration of robust quality data to complement existing measures to facilitate early patient access to medicines. Changes managed through the PQS are subject to regulatory inspection. There is an opportunity for the generation of additional data to support the MAA approval to be managed under the PQS in a similar way that certain quality commitments are managed currently, for example the stability commitment for commercial batches or dissolution testing for the first three commercial batches for applications authorised under Art 10(1) or 10(3). Such an approach could be used to manage generation of additional validation data or extension of shelf life for studies completed in line with the approved stability protocol. **Proposed change:** A new section pertaining to the PQS as a regulatory tool should be added. The document could also benefit from a dedicated section on lifecycle management in general, to ensure post-approval activities are smooth and to some extent covered/addressed in the initial licensing.	Not accepted. As indicated in the text this document summarises the scientific elements and regulatory tools, available in the existing EU regulatory framework. There are already provisions on what can be managed within the PQS. MA dossier requirements are legally binding. As indicated in the document, under certain circumstances it may be possible to defer the submission of some specific data to the post-authorisation phase, but this would be decided on a case-by-case basis and should always be agreed upfront with the agency. The deferral of some data does not mean that these additional data can be managed within the PQS, and not be included in Module 3. Variations and PAMs are toosl to provide post-approval data which should be part of a MA dossier.

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703	6	L703 conflicts with the entire concept of the paper, more specifically the discussion of the use of PAM's as regulatory tools to support the development of accelerated quality packages. PAMs are a suite of tools which can be deployed by regulators on a case by case basis to ensure that in cases where the benefit:risk for the product allows authorisation before the full suite of quality data are available. **Proposed change:** delete line 703. '~~*The intention of PAMs is per se not to facilitate early access or facilitate deferral of data generation.'*~~	Comment noted. PAMs have been added as they constitute a tool which can be used to submit post-authorisation additional data requested by the CHMP during the review.
720	6	"…*may submit missing data*…" Again, the toolbox refers to an incomplete dataset, rather than an alternative data set. If it is agreed with the agency that submission of certain confirmatory data can be deferred until post approval because the assessment of quality, safety and efficacy does not require it explicitly, then this information is not missing. **Proposed change:** *"…may submit the ~~missing~~ additional verifying data as part of the responses to the list of questions or list of outstanding.."*	Comment not accepted. This sentence refers to any data that may be missing at the time of MAA and is requested during the review. It may or not be of verification nature. As indicated in the text applicants should discuss this approach upfront with the regulators to seek agreement on the proposed strategy as there may not be sufficient time in the 2nd round of the evaluation to assess substantial additional data.
723	5	**Proposed change:** ICH Q5E on Comparability of Biotechnological/Biological Products should be added to the list of references.	Accepted.