EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2015
EMA/352692/2015
Pharmacovigilance Risk Assessment Committee

Overview of comments received on 'Good practice guide on risk minimisation and prevention of medication errors' (EMA/606103/2014)

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

Stakeholder no.	Name of organisation or individual
1	Boehringer Ingelheim Pharma GmbH & Co. KG
2	Dr Roberto Frontini, Universitätsklinikum Leipzig
3	Dr Karel van der Warde
4	Joint PDCO/PRAC Working Group
5	Disclosure not permitted
6	Santen OY
7	M. François Pesty
8	Neonatal and Paediatric Pharmacists Group (NPPG)
9	Disclosure not permitted
10	Standing Committee of European Doctors / Comité Permanent des Médecins Européens (CPME)
11	PHARMIG – Association of the Austrian pharmaceutical industry
12	AESGP
13	Gilead Sciences
14	Vaccines Europe
15	Drug Commission of the German Medical Association (DCGMA)
16	Eye-Care Industries European Economic Interest Grouping (ECI-EEIG)
17	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
18	NHS Quality Assurance Committee
19	Novo Nordisk A/S
20	EFPIA
21	German Pharmaceutical Industry Association (BPI)
22	Healthcare Improvement Scotland

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Stakeholder no.	Name of organisation or individual
23	French National Agency for Medicines and Health Products Safety (ANSM)
24	European Generic and Biosimilar Association (EGA)
25	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
26	Novartis Pharma AG
27	European Association of Hospital Pharmacists (EAHP)
28	Dr David Gerret, NHS England
29	The Norwegian Medicines Agency
30	Angela van der Salm, DADA Consultancy
31	Pharmaceutical Group of the European Union (PGEU)
32	Bristol-Myers Squibb
33	Guild of Healthcare Pharmacists
34	Medicines Evaluation Board, The Netherlands
35	Disclosure not permitted
36	Italian Ministry of Health
37	Italian Society of Hospital Pharmacists (SIFO)
38	Philip Lange Møller
39	Disclosure not permitted
40	The Danish National Agency for Patients' Rights and Complaints
41	EMA Geriatrics Expert Group (GEG)
42	Boehringer Ingelheim

1. General comments – overview

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2	Good practice guide on recording, coding, reporting and assessment of medication errors and Good practice guide on risk minimisation and prevention of medication errors as well as Risk minimisation strategy for high strength and fixed combination insulin products, addendum to the good practice guide on risk minimisation and prevention of medication errors are useful documents and fulfill the scope. The addendum to insulin contains the remarks already made. Nevertheless I strongly suggest to add to the documents a list of the used abbreviations. Some of them are common, some are explained but unfortunately not all. Abbreviations are useful but – as remarked in the text – can also be misleading if not clear.	
3	**The question of this consultation:** *'With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in harm during the post-authorisation phase useful taking into account the regulatory remit for risk minimisation measures?'.* Brief answer: Yes, the examples are useful. The examples show the importance of risk minimisation and illustrate medication errors. They directly relate the guideline to practice. However, an analysis of the examples indicates that the guideline suggest that '*adding more and clearer information*' is the main solution to most of the medication errors. This assumption might need to be questioned. **1. Analysis: which examples does the guideline show?** The guideline mentions 30 examples of medicines (active ingredients) that have been used erroneously. Below is a categorization of these examples according to the causes of the errors and risks. • 19 examples are related to the contents and visual design of the information supply. People	

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	can't act appropriately or don't know how to act because information is missing or is overlooked. • 7 examples are related to professional practice. A device, the design, and all information are correct and are available, but human actions are erroneous or pose high risk. Examples are the preparation of parenteral medicines or programming infusion pumps. • 2 examples show problems that are inherent in the design of the medicine or device. It is needlessly difficult for people to act appropriately. • 2 are related to device failure. A device might break or fail. The recommendations in annex 2 present a similar impression of the importance of visual information. Annex 2 lists 45 considerations in 36 bullet points. These can be grouped in two groups: • 34 considerations are related to the contents and visual design of the information supply. • 11 considerations relate to the design of the pharmaceutical form, device design, or the design of outer packaging. Most examples (26 out of 30 examples in the main text (86%) and 34 out of 45 considerations in Annex 2 (75%)) suggest that '*adding more and clearer information*' is the main solution to most of the medication errors. **Some observations about these examples** 1. It might be possible to structure the examples slightly more consistent by providing at least four elements: a description of the error or risk, the consequences, the likely cause, and a proposed solution. In many of the examples in the guideline, some of these elements are missing, which makes the examples less convincing. 2. Some of the examples would be more persuasive when illustrations are added. [For example on page 33/36: The guideline states in line 1167: *"The closure system for containers may be a*	

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	source of error if solutions intend for topical or oral are presented in same way and mistaken for products for injection." A photograph of these closure systems would make it clear what is meant. Now it is vague what this 'closure system' looks like.] 3. There are 0 (nil) considerations related to the reduction of professional errors. There is no guidance on the development and design of educational materials, protocol changes, recommendations, and direct healthcare professional communications (DHPC). This might need a separate guideline: '*How to inform healthcare professionals about medicines.*' 4. There are no considerations on device failure or breakage, or how these could be recognized. This might need a separate guideline: '*How to design devices in such a way that it is possible to check if they function correctly*.' 5. There are no examples that relate to the risk for patients of 'not taking' medicines. Sometimes, these risks are clear for patients (oral contraceptives, insulin), but low adherence figures for medicines for chronic diseases (for example statins) indicate that people underestimate the risks of 'not taking medicines'. If this information is important, than it should be included in both the SMPC and the Package leaflet. 6. The guideline ignores common practices of prescribing and dispensing. For example 'off label prescribing', 'generic substitution, and 'parallel import' do respectively cause 'irrelevant package leaflets because information is not appropriate', 'confusion because the patients receives a product that looks different', and 'confusion because the packaging and leaflet are clearly repacked'. 7. The criteria mentioned in the regulations and guidelines are hard to apply. The recommendations in Annex 2 mention 23 times the word 'clear'. Unfortunately, there is no	

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	standardised way to establish if information is 'clear'. This depends on the contexts, the user, and the activity of the user. The results and consequences of this guideline are therefore very difficult to evaluate for both MAHs and competent authorities. 8. Although there is a lot of advice in the guideline, there is very little that helps MAHs to achieve a reduction in errors and a minimisation of risks. For example: 'Eight examples mention 'confusion caused by packaging or design'. The guideline suggests that: '*applicants should consider the appearance and name of their medicinal product in comparison to medicinal products from other manufacturers used in similar indications, and the potential for confusion between medicinal products.*' (line 609-611). It would be very helpful if the guideline explains exactly *how* this can be done. It is not enough to 'consider' only without taking appropriate actions. A guideline on risk minimisation and prevention of errors might need to include a section with instructions: "In order to avoid any confusion between medicinal products, an MAH must take the following steps before an application.' 9. The guideline does not provide a description of a process or a strategy. It is not possible to evaluate progress, learn from past experiences, or define best practice if there is no description of the activities that lead to lower error rates and minimised risks. The development of the design of medicines, information, and devices might need to be placed within a strategy that consists of a combination of five activities: - Design and redesign (according to best practice, by involving people in the design process, user testing) - Develop systems (reconsider relations, support, responsibilities, …) - Develop, improve, and apply procedures/processes/ protocols and action-sequences that minimise risks and errors - Develop and provide training and educational materials - Develop and improve information.	

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	A strategy that combines these five activities is likely to be most effective. This would require a combination of 'context specific design', 'performance based design', and 'process based developments'.	
5	The document requires a robust link to the requirements for pharmacovigilance, so as not to divert from, the existing provisions or undermine the existing GVP.	
9	We appreciate the opportunity to review the draft of the 'good practice guide on risk minimisation and prevention of medication errors'. In particular we welcome the comments at line 1315 around the need for brand name prescribing and clear and differentiated packaging for biosimilars and their reference products in order to avoid inadvertent switching. Switching from one biological product to another has the potential for unintended consequences (such as immunogenicity reactions) and should only occur at the request of the prescriber and based on sound medical judgement as described in Questions and answers on biosimilar medicines (similar biological medicinal products) EMA/837805/2011. Furthermore, we are confident that brand name prescribing will allow for improved traceability in the event of an ADR as per the reporting requirements of the so-called PV legislation (Directive 2010/84/EU and Regulation (EU) No 1235/2010). In addition, we consider that the need for clear packaging constitutes not only the primary and secondary labels but also the SmPC and the PIL, the information source which allow prescribers and patients to make informed choices regarding their medication. For biosimilars information on statement of biosimilarity, unique warnings and precautions, unique safety signals, and relevant data from comparative clinical trials including information on immunogenicity profiles should be clear in the SmPC to allow healthcare professionals to make informed choices around the products they prescribe as described in section 6.1.2.2 (line 545 onwards). The current lack of granularity provided in the product label for biosimilars could lead to products being confused for one another and therefore inadvertent interchange at the prescribing level. Finally we welcome the use of distinguishable names including brand/invented names for biological medicinal products as described in the section on naming (6.1.2.1) and on the use of	

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	new technology in avoiding medication errors (6.1.4) and look forward to open discussion with all stakeholders as these important topics are discussed and as they interact with other legislation such as the Falsified Medicines Directive and the WHO proposal for a biologics qualifier.	
11	It should be considered to propagate this information also to prescribers and pharmacists since many cases of medication errors result from insufficient, misleading or wrong information of patients.	
11	Marketing authorisation holders are surely the ones to be the most easily compelled to adhere to guidelines, they are, however, probably not the ones to gain the most knowledge about medication errors, especially those without ADRs (ME – ADR). In this respect the content of this Guideline should be reconsidered. We agree that participants of the health system that are not directly affected by the above regulations (prescribers, dispensers, other health care professionals), are the right target audience when striving to reduce patients' risks deriving from medication errors. But we suspect that these audiences are not adequately reached by this Good Practice Guide.	
12	This good practice guide provides key principles of risk management planning in relation to medication errors; however it does not provide practical recommendations on how to identify potential for medication error during product development. Recommendations related to reporting of medication errors and route cause analysis are not fully applicable with non-prescription products (OTC environment), especially regarding intercepted errors and potential errors as most of the report are received from patients/consumers. This guidance should also be based on practical examples of medication errors which can happen with non-prescription medicines bought by consumers without Health Care Professional (HCP) advice. • The organisation of subsection in Section 5.2 is confusing.	

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	o Suggest to follow change title of section 5.2.3 to “Tools for identification of medication errors during pre-authorisation phase” o Section 5.2.5 is a list of examples of medication errors. Would suggest moving all examples into an Annex as done for medication errors related to product design. • Section 6.1 is a copy/paste of GVP Module XVI. We would suggest summarising the most important concepts and referring to the GVP Module.	
14	This guideline on ‘…prevention’ of medication errors (ME) should not leave out the fundamental issue of preventability which is a characteristic of MEs. However, the question about whether or not an ADR was caused by an ME and could have been prevented can usually not be answered in an adequate way by ‘yes’ or ‘no’ but by a term expressing the likelihood on a scale – in analogy to terms like ‘certain’, ‘probable’ and ‘possible’ used in causality assessment of classical (not ME-related) ADRs. There is ample literature on the assessment of preventability and scales for expressing grades of its likelihood (e.g. Hakkarainen et al. Drug Saf 2012; 35(2):105-126). This literature and the underlying concepts should be addressed.	
15	Members of the ECI-EEIG welcome the initiative of the EMA to provide guidance on how to minimise risks and to prevent medication errors. In Annex 1 of this Good Practice Guide, “Sources of medication errors in medicinal product design”, examples of product designs are given that led to errors in the administration of the medication, and in some instances causing serious harm to the patient. While most of the examples were subject to assessment by regulatory bodies, including the EMA and NCAs, it has to be assumed that corrective actions were taken or at least are underway. However, by citing actual examples that allow the identification of the medicinal product and of the pharmaceutical entrepreneur, the impression is left that these examples cause a greater risk than those that are referred to in general terms.	

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	Therefore, members of the ECI-EEIG propose to modify the wording in Annex 1 such that medicinal products and pharmaceutical entrepreneurs are not easily identifiable.	
18	As there for all medicinal products will be a potential for medication errors, it is important to specify that it is only those medication errors considered an **important** safety concern that should be captured as important risk.	
20	The content of this Good Practice Guide is very broad, i.e., a wide range of scientific disciplines are covered and the level of detail regarding expectations is not always clear. Also , the design of the medicinal product as reflected in 5.2.1 and in Annexes 1 and 2, is done in accordance with GMP guidance and similarly, product labelling/information is guided by QRD guidance documents. There is considerable overlap between the guidance provided in this document and other non-GVP sources with the potential for misinterpretation by all stakeholders as to roles, responsibilities and accountabilities A suggestion would be to add an Annex to this document summarising the role of the different stakeholders involved in risk minimisation and prevention of medication errors (i.e. MAH, Healthcare Professionals, Authorities, etc.) with a reference to the relevant parts of the main document. Clarification is requested on the expected content pertaining to medication errors in relation to the dossier and in the risk management plan. Given the broad scope of the guidance and that it addresses many different stakeholders it is unclear how these recommendations/requirements will be implemented and evaluated. We would therefore appreciate further discussions at one of the upcoming authority/industry meetings before finalizing the good practice guide.	

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20	There is inconsistency in the definition of medication errors between this guide, the 'conceptual definition' of a medication error proposed in the other draft medication error guide and GVP Module VI. Consistency and clarity in the definition of a medication error between documents is requested. Also there is inconsistency throughout the document in the processes involved in medication errors. • Line 70-71, medication error is included as: 'is considered to be any unintended failure in the medication process, including the **prescribing, dispensing, or administration of a medicinal product'**. • Line 79, it is considered to be any unintended failure in the medication process, including in **prescribing, dispensing, preparation or administration of the product**. • Lines 125-127, the process includes: **prescribing, dispensing, preparation for administration, administration and provision of information**. Furthermore, the Guide for Reporting, Assessing and Recording Medication Errors includes **monitoring (prescribing, dispensing, preparation, administration or monitoring…**.). Consistent with the Institute for Safe Medication Practices (ISMP) best practice guidelines (http://www.ismp.org/Tools/guidelines/default.asp, and associated list of error-prone abbreviations; accessed 19 May 2015), consider adding a statement that all measuring devices should use "mL" as the unit of measure. It is recommended that oral liquid dosing devices should only display measurements using the metric system. In addition, if patients will take an oral liquid medication after discharge, they should be supplied with oral syringes of an appropriate volume marked in mL (or provide a prescription for oral syringes), to enable them to measure oral liquid volume in mL. Consider the development of common pictograms/pictures (i.e. concerning the type of population (child, adult), route of administration …) for the PIL/labelling, in order to improve the understanding of patients and thus help to avoid some potential medications errors(Similar to the type of pictograms which could be inserted in a PIL following a readability test)	

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21	We appreciate the efforts of the PRAC to improve patient safety regarding medication errors. Nevertheless, although Directive 2001/83/EC and Implementing Regulation EU 520/2012 form the legal basis for this Good Practice Guide the content is mostly aimed at participants of the health system that are not directly affected by the above regulations, e.g. prescribers, dispensers, other health care professionals. We agree that these professions are the right target audience when striving to reduce patients' risks deriving from medication errors. But we suspect that these audiences are not adequately reached by this Good Practice Guide. The requirements for the Agency, member states (competent authorities) and MAHs are sufficiently addressed by the above referenced statutes and the respective GVP modules. Insofar, the present Guide does not lead to a further improved patient safety.	
21	We would not consider the examples useful taking into account the regulatory remit for risk minimisation measures. Most of the examples are beyond the area of influence of the stakeholders to which this Guide is addressed.	
22	Overall support of this good practice guidance and it is good to see a focus on learning from errors to reduce harm. Some suggested changes are detailed below.	
23	ANSM proposes to clarify for whom the guide is intended and to -organize differently the guideline. **The following plan could be proposed:** <u>The definitions and types of medication errors</u> - See Annex 1 below <u>The roles of the applicants / marketing authorization holders (MAH)</u> - Before the marketing authorization: the applicant should identify the potential risks of medication error and propose minimization measures using a risk analysis method. - After the marketing authorization: identify and analyse risks of medication error and propose measures concerning modifications of drug design, the medical information (SmPC, leaflet) and / or to develop risk minimization tools, and then assess its impact	

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	(PASS studies, questionnaires ...) A check list for applicants, when requesting a MA, could be proposed for all measures available to minimize risk. <u>Proposition of risk minimization measures of medication errors:</u> - MAH should be requested to provide unitary package (with number of batch and expiration date) in order to limit risks of errors between 2 drugs for example. - The SmPC and leaflets should be clear and harmonized regarding the reconstitution, stability and method of administration. - Several leaflets should be provided in hospital packagings in order to ensure correct information for all users. - Regarding labelling, MAH should be encourage to highlight the common name, INN, (increasing font size) and not the brand name. - MAH should be encouraged to provide forms adapted for people with swallowing problems and to mention in Smpc and leaflet if crushing is possible. **Annex 1 - Types of medication errors** <u>Initial stages of the occurrence of medication error</u> - Error of prescription - Error of dispensation - Error of extemporaneous preparation of a medicine - Error of administration - Therapeutic monitoring error <u>Nature of medication error</u> - Error of medicine - Error of dosage - Error of route of administration	

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	- Delivery rate error - Patient error - Error of time of administration - Technical Error - Duration of administration error - Error of omission - Pharmaceutical form error - Expired drug, damaged or poorly preserved <u>Causes of medication error</u> - Similarity of the outer packaging - Similarity of primary packaging - Similarity of commercial / brand names - Similarity of the tablets / capsules - Lack of readability of the information labelling - Missing information, erroneous or confused - Inadequate presentation - Computerized system for prescription assistance - Human error made by a patient or loved one - Human error made by a health / professional caregivers - Lack of organization within the drug circuit	
24	Similarly to the information in Annex 1 where sources of medication errors based on design are presented, a systematic overview of medication errors that occur at different stages of a medication process (i.e. prescribing, dispensing, administration etc…) in a separate annex would be welcome. Furthermore, for each of these stages a clear guidance on how to prevent the medication error for each stakeholder involved in a particular process would be even more helpful.	
24	In addition, again following the examples of Annex 1 medication errors, it would be of an added	

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	value if medication errors related to health systems would be provided in a separate annex, in order to have a clear overview.	
24	Although it is valuable to present examples of medication errors related to the health system, in our opinion, guidance should primarily provide clear input for the industry and regulators on the sources and types of medication errors that could be prevented by implementation of risk minimization measures by pharmaceutical company (name, packaging, clear instructions on posology etc.).	
24	It would be helpful if you could provide a link where different literature references mentioned in the document could be found. Additionally, some pictures of examples of some terminology used in the guide would be very helpful, e.g. livery.	
25	**Introduction:** The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), recognising that medication errors present a major public health burden, welcomes the opportunity to respond to this consultation. EUCOPE is Europe's principal trade body for small-to-medium sized innovative companies working in the fields of pharmaceuticals and medical devices. EUCOPE represents more than 900 member companies through direct affiliations and via its member associations such as the German Pharmaceutical Industry Association (BPI), the British Ethical Medicines Industry Group (EMIG), France Biotech or the Swedish Association IML. Many of the members are companies focused on research in new orphan therapeutic areas with no alternative treatments, e.g. Actelion, Alexion, Biogen Idec, BioMarin, Celgene, Intercept, InterMune, Orphan Europe, Otsuka, Sobi and Vertex. Within this response we would like to focus on a particular issue which impacts our members and patients alike and which we believe should be further highlighted: the off-label use of	

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	medicines. Off-label prescribing can lead to an increase in medication errors and, therefore be limited to specific circumstances so as to not undermine the EU regulatory framework for pharmaceuticals and ensure the high standard of patient safety, which the establishment of the EMA and the centralised authorisation procedure have maintained. **Off-label use** Any medicine intended for market approval in Europe must undergo a rigorous analysis of its safety and efficacy in the disease population in question. Approval of a medicine for specific indications is the outcome of an extensive analysis of the benefit versus the potential risks posed by that medicine in a specific patient population for specific indications. The robust European regulatory framework is there to safeguard patient safety and minimise medication errors by providing clear guidance on how a medicine must be taken within the label. As indicated within the consultation one of the key “routine risk minimisation measures which apply to all products” is precisely the “labelling” of the product. **Medicines prescribed off-label immediately circumvent this risk minimisation measure.** At the moment, off-label medicines are often prescribed at the discretion of physicians on the basis of the medical need of the individual patient. While this is an acceptable practice, in cases where there are no alternative on-label medicines available on the market and the disease is severe, there are no specific guidance indicating when off-label prescribing should be allowed and when it should be avoided to mitigate patient risk. In addition, some European member states have begun promoting off-label use of medicines simply for economic purposes in indications where there are approved medicines available. Not only does this undermine the EU regulatory framework, it puts patients at risk. We should be	

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	reminded that under EU law, the supply of medicines for unauthorised uses is an exception to the requirement that a medicinal product should either have a MA or be used in the context of a clinical trial. **<u>How off-label use increases the risk of medication errors</u>** Promotion of off-label use by healthcare bodies bypasses and indeed undermines the rigorous regulatory approval process, which is designed to ensure patient safety and limit medication errors. Off-label use promotion for pure economic reasons raises serious concerns over patient safety as it is promoting the use of medicines in indications **for which the competent regulatory authorities have not performed a risk-benefit analysis** following established safety and efficacy criteria. Off-label use is also often associated with compounding by physicians or pharmacists in order to adapt the doses of the product to the specific indication for which it is being prescribed. This increases the chance of prescribing errors which, as the consultation indicates, “may relate to stipulation of the wrong drug, dose, strength, and indication, route of administration/pharmaceutical form or length of treatment”. Given the higher risk levels associated to the use of medicines off-label, EUCOPE believes that this should only be accepted in very specific circumstances when the patient is suffering from a severe disease for which there is no available on-label alternative. **<u>Under-reporting of medication errors as a result of off-label use</u>** Another concern related to off-label use and closely linked to medication errors relates to the reporting of adverse events.	

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	The promotion of off-label use by healthcare bodies can create uncertainty with regards to product liability, in particular with regards to who would be accountable for safety issues associated with the off-label use. While not yet documented, it is plausible that physicians may under-report side effects when using off-label products as a result of this uncertainty regarding liability. Automatically, this can make it more challenging to identify medication errors where they have occurred. **Recommendation to the EMA** Given the potential negative impact which off-label prescribing can have on patient safety and medication errors (in particular when driven by economic reasons) EUCOPE believes that the EMA should address this issue, either in adopting the referred guideline or developing a separate guideline on off-label/unlicensed use of medicines to ensure their use is limited to the following specific circumstances: • The disease is severe or life threatening; • The standard treatment has failed or is not available; • There are no other on-label treatments available on the market; • Some evidence already exists in the literature; • The patient has been informed by the physician that the product is being used off-label; • Physicians are responsible for reporting side effects.	
26	Novartis Pharma welcome the opportunity of commenting on the document, but notes that it is generally unclear throughout the guidance document which “devices” are in scope of the	

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	document and which requirements apply to which category of device/drug “combination”. It would be worthwhile to use outline the scenarios, i.e.: • medicinal products forming a single integral product with the device and not-re-usable • medicinal products forming a single integral product with the device and -re-usable • medical devices co-packed with the medicinal product • medical devices not provided with the medicinal product but intended to be used for the administration of the medicinal product, and explain which requirements already exist and how they shall be bridged to the risk minimisation and prevention of medication errors of the medicinal product. Novartis also suggest that more detailed guidance is provided for co-packed medical devices and for example describe the link between the medicinal product RMP and the medical device risk management file as well as the medical device post-market surveillance plan. The synergy between device and medicinal product regulations could be improved throughout the document.	
27	The European Association of Hospital Pharmacists (EAHP) supports the EMA initiative to publish a good practice guide on risk minimisation and prevention of medication errors. Overall, EAHP: 1. Recommends the guidance go further in some areas; 2. Make some suggestions for presentation improvement; and, 3. Highlights some other aspects for EMA reflection in respect of risk minimisation and prevention. **1) Areas where the guidance should go further** In many areas of the document, the EMA has correctly identified areas of risk, but seems reticent in expressing solid points of guidance and recommendation.	

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	A) Reducing prescription error by eliminating hand written prescriptions The Guidance is correct in highlighting the risks of error inherent in handwritten prescriptions, and the calls by international organisations for the elimination of hand written prescriptions. EAHP also calls for universal use of electronic prescription for this, and many other reasons[1]. EAHP therefore consider that a more explicit statement that the EMA giving the Agency's specific call for the elimination of handwritten prescriptions would strengthen the impact (and therefore value) of the guidance document. As currently drafted, EMA support for electronic prescribing might only be indirectly inferred from the document. *B) Tools for improving product design* See below lines 209-211. *C) Preventing dispensing errors* See below lines 317-335. *D) Potassium Chloride* See line 346. **2) Suggested areas for improving the presentation of the guidance**	

[1] http://www.eahp.eu/press-room/eahp-members-call-universal-use-electronic-prescribing-europe

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	A) Further use of visuals Overall, where parts of the guidance document are supported by visual illustration the content and messages conveyed are strengthened and enlivened to the reader. There is therefore scope for increasing the value of the guidance by similar efforts in other areas. *B) Better highlighting of specific recommendations* Where the document does make clear recommendations these should be made more evident and obvious to the reader by being in bold or similar form of differentiation from the standard text. Without this, it can be hard to identify what the actual guidance in the document is, as opposed to explanatory and background information. A summary of the guidance document's recommendations would also be helpful, either at the start or end of the document. *C) Annex 1 on sources of medication error in medicinal product design* See below line 1036. **3) Other areas for reflection in respect of risk minimisation and prevention** *A) Risk minimisation benefits from bar coding medicines to the single unit to achieve bedside scanning practices* In the overall area of risk minimisation, EAHP wishes to bring to the attention of EMA the solutions that can be provided by the introduction of bedside scanning technologies. Operating	

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	alongside Computerised Prescription Order Entry (CPOE) systems, and by enabling a final check at the point of administration, it can mark an important advance in ensuring the right medicine is administered to the right patient in the right dose at the right time by the right form of administration. More information is available here: http://www.eahp.eu/practice-and-policy/bar-coding-medicines-to-the-single-unit However, due to the nature of medicines use in hospitals, where medicines are frequently split from their original containers, to operate effectively a bar code is required on the single unit of the primary packaging of the medicine in order for nurses to be able to conduct the final scan at the bedside. Sadly, medicines in Europe are not systematically barcoded in this manner at the point of manufacture, often therefore requiring hospitals to re-label medicines with such bar codes. This can be costly and resource intensive making the patient safety advances of bedside scanning hard to reach for many hospitals in Europe. EMA support for the achievement of single unit bar coding of medicines at the point of manufacture would therefore be valuable in respect of the overall goal of the guidance document – improving patient safety and reducing risk associated with medication use. EAHP considers that formal support by EMA for the achievement of bar coding of medicines to the single unit to achieve widespread practice of bedside scanning is within the remit of the EMA in respect of supervising the safety of medicines in the EU after they have been authorised. *B) Greater onus on picking errors* EAHP consider that the risks posed by picking errors are underemphasised overall within the	

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	document. Regulatory authorities have an important role to fulfil in ensuring safe labelling practices that prevent picking errors, rather than facilitated e.g. by indistinct description or differentiation between concentrations and/or volume. *C) Other areas for potential inclusion and expansion in the document* The role of the hospital pharmacist in relation to patient safety and the prevention of error was a major area of consideration during the 2014 European Summit on Hospital Pharmacy. This two day event brought together representatives of hospital pharmacy from across Europe as well as European healthcare professional and patient organisations in order to jointly determine 44 Statements about the future of medicines use processes in European hospitals Recommendations within those statements that have relevance to the scope of this guidance document include: • Seeking **review of medicines use processes** in hospitals by an external quality assessment accreditation programme (Statement 5.3); • Decreasing the risk of medication errors by disseminating **evidence-based approaches** to error reduction including computerised decision support (Statement 5.5); • **Identifying high-risk medicines** and ensuring appropriate procedures are implemented in procurement, prescribing, preparing, dispensing, administration and monitoring processes to minimise risk (Statement 5.6); • Promoting guidelines that ensure that medicines administration processes are designed such that **transcription steps** between the original prescription and the medicines administration record are eliminated(Statement 5.7);. More information is available here:	

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	http://ejhp.bmj.com/content/21/5/256.full.pdf+html. We urge the document authors to consider including such recommendations within their final guidance.	
28	Overall I would agree with the direction of travel. My major comments are that: a. this document makes no mention of formal system barriers that are introduced by member states Patient Safety Organisations (PSOs) to minimise risk to patients by making it harder for Healthcare practitioners to do the wrong thing. The whole focus is on the Authorisation Holders (MAHs) responsibility and not responsible bodies for developing system barriers in practice. For example the introduction of non-leur neuraxial connectors, the requirement for dedicated enteral feed connectors, and removal of strong potassium (>40 mmol/l) from areas where inadvertent improper injection was more likely. Clinical practice is playing 'catch up' with error-prone products and introduces system barriers to counter latent errors. It would be far better to have an integrated approach where MAHs, Competent Authorities, PSOs and clinical practice amalgamated to pave the way for safer introduction and use of medicines for patients. This implies far more formal links between MAHs, Competent Authorities and National PSOs. There is a recognition of this in the document 'Good practice guide on recording, coding, reporting and assessment of medication errors (line 171)', however, I believe it need to be far more 'in scope' and mainstream; b. that the documentation demonstrates a necessary serious commitment for integrating post-Authorisation error reports such as those captured by local risk management systems and national organisation (such as NHS England and the National Reporting and Learning System) with the MAHs' Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) and ultimately the Summary of medicines Product Characteristic (SmPC). It is mentioned in line 431-3, however, it should be much stronger. There are a raft of systems in place in practice that routinely risk assess the	

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	use of medicines in practice, producing reports and guidance for healthcare practitioners. This wealth of information needs to be captured and used through the Competent Authority and MAHs to improve the safety of medication products used. As a corollary, the PSURs should be made available to those in authority for introducing system barriers (see a.); and, c. it is not possible for FMEA to fully predict or pre-empt all the errors that will occur in practice. Despite the expertise that exists within the Competent Authorities, the EU, the EMA this cannot be the only mechanism relied upon. As a suggestion, the Phase 4 pre-authorisation for products should include a mandated, formalised feedback from healthcare practitioners with 'safety-in-practice credentials'.	
28	With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in harm during the post-authorisation phase useful taking into account the regulatory remit for risk minimisation measures? Answer: 'Useful' yes, but not exhaustive. Medicines are used in complex settings on patients with co-morbidities and idiosyncratic reactions. We can only hope to pick up patterns of errors in this environment. And from such understanding implement individual actions for safer practice. We will never completely eradicate error where human intervention is involved, but we can minimise it. The more we add to the examples (5.2.5) the better armed we are to 'pave the way for safer introduction and use of medicines for patients'.	
29	Relates to both line: 292-305, 312-316, 318-326 Section 6.1.2.1"Naming" and section 6.1.2.2 "Labelling and livery", line 710 and 1042: The Norwegian Medicines Agency has over time received several reports on mix up between immediate release formulations and modified release formulations/depot. It is especially the name setting of "INN+ MAH" that in an electronic prescription setting puts the prescriber in	

Stake-holder no.	General comments	Proposed change by stakeholder, if any
	danger of picking the wrong line – especially the name setting INN+ MAH for tablets that comes in both immediate release and modified release formulations. Recent examples are the oxycodone tablets (immediate and depot), where a mix up of these formulation may have serious consequences. We would like to challenge if there may be developed a standard suffix or name-setting for the modified release formulations to more easily distinguish the formulations – also by name. At patient level and HPC handling the mix up may potentially also be reduced by a standard design feature to be present on the labelling for the modified release products	
29	Ref 1105. Patches with different modified release rates may cause medication errors by the name-setting “Inn + MAH”, which makes it more difficult to distinguish the different products.	
30	Reply to question (line 14): I think the examples are useful to clarify the potential errors. The ones presented are known and referred to in other publications. “regulatory remit” to me is not clear.	
32	With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in harm during the post-authorisation phase useful taking into account the regulatory remit for risk minimisation measures? **Yes, the examples of medication errors as well as the risk minimisation strategies are useful. GVP RMP module V proposes 4 broad categories of medication errors: wrong medications, wrong dose, wrong route of administration, and wrong patient. The examples in chapter 5.2.5 provide a broad range of examples of medication errors to add clarity to these 4 broad categories and will help assure uniform reporting. It should be noted that these are only examples and other medication errors might arise and other risk minimisation strategies may be developed depending on the product and consequences of the medical errors.**	
33	Need to include errors due to the use of information on apps eg amphotericin comes as 3	

Stake-holder no.	General comments	Proposed change by stakeholder, if any
	formulations and 3 people were killed because the junior doctor looked at their smart phone for prescribing information and only thought there was one formulation.	
34	The document is quite lengthy and a more concise document would be appreciated. The size (36 pages), the lay-out, the length of some sentences and the mix-up of theory and examples make it difficult to comprehend. In addition, a large number of typing errors have been noted, which should be corrected. Adding these aspects to the specific (i.e. scientific and regulatory) comments detailed underneath, a major revision of the document is urgently requested.	
34	Currently, the relationship with other EMA quality provisions is not clear, whereas some differences with published ICH/EMA guidelines, reflection papers, Q&A documents and the Ph. Eur. have been identified in relation to pharmaceutical matters. In addition some new concepts have been introduced where it is not clear what they would mean e.g. clean break-mark. In conclusion, the relationship and consistency of this guide with other regulatory provisions would need increased attention.	
34	The document discusses many issues related to the pharmaceutical design of medicines i.e. aspects related to Module 3 assessment. For this reason, involvement of the QWP and BWP is suggested in the guide's finalisation process. This may also help to assure the consistency of both guides with the existing quality provisions. In any case, it should be clear if the current CHMP position paper on medication errors will be kept, revised of withdrawn.	
34	With regard to the definition of medication error, it is not considered sufficient to only refer to the guide on coding and recording of medication error. It is recommended to add the definition of medication error at the beginning of this document and to conform that all examples on medication errors are meeting this definition. The current wording further aids to the confusion on the definition of medication error (at least for pharmaceutical assessors). By including a clear definition at the beginning, the number of examples throughout the document can be limited. Reference is made to the comment on this aspect (definition of medication error) in the MEB	

Stake-holder no.	General comments	Proposed change by stakeholder, if any
	comments to the EMA draft guide on recording, coding, reporting and assessment of medication errors	
34	The PRAC is reminded that medication errors may not only be substance related, but rather trademark as the excipient composition, tablet size etc may differ among companies.	
37	We would like to suggest some concerns about the drug stability after the reconstitution. Some drugs (as for example Docetaxel) produced by different pharmaceutical company have different stability. I can understand that different excipients can be responsible for the different stability, for example, Docetaxel has a different content of ethanol according the different product. Considering that in the hospital it is possible to change product according the tenders, how this variability can influence the patient response and safety, especially regarding the possible different stability? (See FDA warning box). This variability can influence standard preparation processes. While pharmacists are aware of this variability, when a drug is prepared in the ward, it is very difficult to monitor it. It is important to take in consideration the relevance on the information present on the drug package inserts. In particular, for the stability of intravenous drugs compounded by the pharmacy or in the wards there is a lack of information on drug stability according the concentration used, the dilution or the containers used (syringe versus bottles or bags). For other drugs as drops or syrups sometime is not preset the stability after the opening or the conversion between mg or ml and the number of drops creating an high risk of medication errors.	
41	**Recording, coding, reporting and assessment of medication errors** Create a list of medications with high risk potential Differentiate between sound-alike and look-alike medications (pay attention to separate	

Stake-holder no.	General comments	Proposed change by stakeholder, if any
	storage) Record carefully all medications: importance of in-depth medication review (history taking followed by evaluation of medication used) as the first step Register substitution of medications taken at home during hospital stay Seamless pharmaceutical care: assure information flow between different settings (and different ward during hospital stay) regarding medications prescribed in addition to medication related problems in general and medication errors in particular **Minimisation and prevention of medication errors** *Communication* during hospital stay: including standard procedures, information about the patient, multidisciplinary team discussions *Medication process*: apply hospital formulary, farmacotherapeutic guidelines, unit doses dispensing system, electronic patient history including medication module, bar-coding of medications, availability of medication information for the patient and for the carer, administrative procedures about prescribing, preparation and administration of high risk medications (i.e. cytostatics), process controls *Teaching and education*: multidisciplinary team discussions, risk management, education courses in the hospital, educational courses for new collaborators, continuous measurements and follow-up reporting of potential or already happened errors *Practical problems with medication use*: a classification of the practical problems experienced by older people (ranging from problems with reading and understanding the instructions for use, handing the packaging, completing any preparation prior to use to taking the medicine). *Safety information* about older people is vital. Information about age-related differences in ADEs and drug-disease interactions is important. Information about the *effectiveness of the drug* in older people is needed. Information about age- related differences in efficacy and in dose-response should be included. Information about time to benefit in the older population is valuable.	

Stake-holder no.	General comments	Proposed change by stakeholder, if any
	Information about *convenience of use* by the patients is important to prescribers. The availability and applicability of information relevant for appropriate prescribing to older people in SmPCs should be assured.	

2. Specific comments on text

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
1	531-532	Comments: BI is aware about name confusions between **Pradax** and Plavix in Canada before 2013, and has also reported these to the EMA in the PSUR and RMP: • During the initial submission of Pradaxa in Canada, Health Canada did not accept the BI proposed trade name Pradaxa and requested a change to Pradax, which BI accepted. • Later on, cases of name confusion between Plavix and **Pradax** were reported from the Canadian market. • As a consequence Health Canada requested BI to change the trade name from **Pradax** to **Pradaxa**, which was then implemented by BI starting in January 2013 • As imposed by Health Canada in the context of the trade name change from Pradax to Pradaxa, BI has submitted for 2 years 8 quarterly reports evaluating any medication errors world-wide caused by name confusion (calendar years 2013 and 2014). This follow up measure has now been completed with the conclusion not only for Canada but for world-wide markets, that the received data do not support an unexpected level of confusion between Pradaxa and any other drug. Based on the available data, no risk minimisation activities are considered necessary. • BI is not aware of any further name confusion cases for Pradax**a** and Plavix Unless the EMA has additional information, which BI is not aware of, BI kindly requests that the Pradaxa example is deleted from the draft guideline. Alternatively, the guideline could clarify that the	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		name confusion pertained to Pradax (an outdated local Canadian trade name) and Plavix and not to Pradax**a** and Plavix. In the case EMA has additional information on cases, which BI is not aware of, BI would be interested in learning more about these cases.	
1	300-305	On April 14th, 2015 the Agency published the draft "Good practice guide on risk minimisation and prevention of medication errors" (EMA/606103/2014) for consultation. In section "5.2.5. Medication errors resulting in harm during post-authorisation phase" of this draft document (p.11) the below pramipexole example is provided. Since only the INN pramipexole is stated, may I kindly ask you to clarify whether this example refers to Sifrol/Mirapexin, or to experience gained from generic pramipexole? In case experience gained from Sifrol/Mirapexin is being described, the MAH of Sifrol/Mirapexin, Boehringer Ingelheim International GmbH (BI), is concerned about the way information is being presented implying a causal relationship which seems to be incorrect. Provision of wording in the SmPC and Package Leaflet stating to not chew, divide or crush the prolonged-release tablets and to swallow the prolonged-release tablet whole was not triggered by reports about accidental overdose, when Sifrol/Mirapexin prolonged-release tablets were crushed for ease of swallowing. Such warning statement was already contained in the initial submission of line extension application EMEA/H/C/133,134/X/51,59.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		Furthermore, we are not aware about any cases of overdose due to crushing of Sifrol/Mirapexin prolonged-release tablets. In case the Agency has additional information which BI is not aware of, BI would be interested in learning more about such potential cases. Likewise, redesign of the outer packaging for better differentiation between the two formulations was not triggered by reports about incorrect dosing with Sifrol/Mirapexin when the immediate-release formulation was mistaken for the prolonged-release formulation. The theoretical risk for dosing error (3 times versus once daily intake of the prolonged-release formulation) was intensively discussed during line extension procedure EMEA/H/C/133,134/X/51,59 and led to revision of the main colour scheme of the outer packaging design to better differentiate between the two formulations. Additionally, in that same procedure the statement “once daily” in red colour was prominently added to the outer packaging of the prolonged-release formulation. In conclusion, unless the example originates from generic pramipexole or EMA holds additional information, which BI is not aware of, BI kindly requests that the pramipexole example is deleted from or appropriately revised in the draft guideline.	
4	794-842	Please note that these comments on section ‘6.2.1. Paediatric patients’ are mainly additional information in order to focus this section a bit more on paediatric related aspects. The additions made from the working group include the following information: • Dose ranges and under dosing • Risk of volume overload and over concentration	Paediatric patients may be at particularly high risk of medication errors due to their variation in age, size and weight, body surface area (BSA) and degree of development. This is reflected in the dosing instructions for some paediatric products which express dosage and strength by bodyweight rather than by age in months or years. Overdose was the most commonly reported medication

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		• Need for indication of a minimum volume for dilution • Need for caution with the excipient in paediatric formulations • Expansion on the specificities related to neonates and the increased risk for toxicity based on physiology parameters • Prevention of accidental ingestion for certain medication types • Need for secured child resistant containers	error (accounting for 21% of all reports) in a study of paediatric patients (Manias et al 2013[24]) while underdosing in certain paediatric specialties was the most commonly reported medication error in these settings (Bolt et al 2014[25]). It should be noted that in some cases, when dosage is recommended in ranges, there is a tendency of administering the dose from the lower value of the recommended range due to the fear of overdosing. These opposite yet complimentary findings indicate a more general risk of dosing errors (leading to either over- or underdosing) in paediatric patients. Paediatric prescribing is often determined by the patient's weight, yet weight is not measured before each prescription and can change over time meaning that recalculation of drug doses is required. Due to the need to find the right dose based on weight (or BSA) for the majority of paediatric medicines, mathematical miscalculations may be more likely in paediatric patients than adults. In this calculation, it should be ensured that the total dosage calculation based on weight (per kg) does not exceed the maximum adult dose (either single or max. daily dose). Occasionally there is a need for complex dilutions by medics/nurses/pharmacists; medication errors with infusion of fluids and electrolytes are common. The risk of volume overload should be taken into account, as well as the risk of too high concentrations with small volumes. For liquid oral medications there is some evidence that oral syringes may be the most accurate dosing device. However, liquid formulations may present a risk of

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			medication error if the wrong dosing device is used to deliver them (e.g. a liquid oral formulation of paracetamol was presented with a dropper graduated in mL for infants less than 3 years and an oral syringe graduated in mL for infants older than 3 years; use of the oral syringe in infants could lead to a risk of overdose). To avoid dosing errors, minimum volume for dilution should be indicated, takin into account the risk of overload. Attention should also be paid related to excipients (sodium/potassium) in effervescent dosage forms. Morerover, caution is needed with small volumes, i.e. tablespoon or teaspoon. Measuring by syringes of preferred. Historically there has been a lack of development of paediatric medicines and lack of clear guidance on paediatric dosing in product information or other sources, leading to off-label use of medicinal products with indications in adult populations. The situation has improved with the introduction of the paediatric regulation in 2006 (Regulation (EC) No 1901/2006) that places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. However, the ongoing limited availability of paediatric formulations may lead to misuse of product formulated for adults. The EMA workshop on medication errors noted that the risk

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			of medication errors is particularly high in specific paediatric groups such as neonates, where age-specific dosing requirements are based on the known influence of ontogeny on the disposition of drugs. The weight of neonates may change rapidly over a short period of time, making the appropriate dose adjustment critical. Differences in the pharmacokinetic (PK) profile of neonates compared to that of older children probably contribute significantly to them being at higher risk of overdose and being less able to tolerate a medication error than older patients. This is largely due to their still-developing hepatic enzyme systems and renal systems, both vital for metabolism and clearance, as well as the variable absorption, delayed gastric emptying and reduced gut motility in neonates. In addition, gastric pH is higher in neonates (decreasing to the adult level at the age of two), therefore there is a lower bioavailability of alkaline medications and higher of acidic ones. When applied transdermally, absorption of the medication depends on skin thickness and perfusion. At birth dermis is normally only around 60 % of its adult thickness and maturation takes 3-5 months after birth. In neonates relative body surface is greater than the body mass and there is increased permeability and thinner *stratum corneum*, which can result in higher absorption of medicine, especially in febrile state. In neonates, there is a decreased value of methaemoglobin reductase, therefore with higher absorption and repeated

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			use of local anaesthetics in the form of cream, methaemoglobinaemia could occur. In neonates there is a lower concentration of albumin and alpha-1-acid glycoprotein as well as reduced binding affinity. Consequently, there is a higher level of free drug as well as quicker passage through the biologic barriers which can result in possible toxicity. In addition, in neonates the blood/brain barrier is immature and relatively insoluble medications (morphine) are passing more quickly to the CNS than in adults. Apart from neonates, the risk of medication errors in paediatric patients may also be increased in circumstances where high risk medicines, specific drug combinations and formulations are used, or where untrained healthcare workers are involved, and in transitions of care such as admission and discharge. Paediatric patients with chronic conditions and/or complex medication regimes (e.g. children with learning difficulties, oncology patients) may also be at particular risk of medication error due to the added complexities of dosing or polypharmacy in these patients. Consideration should also be given to the prevention of accidental ingestion (medications in a form of lolly pop, chewing gums, patches) or other unintended use of medicinal products by children. Therefore special attention should be paid in securing child resistant containers and careful disposing. A standard statement that medicinal products should be kept out of the sight and reach of all children is included on the labelling for all medicinal

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			products and in practice the use of locked containers or medicine cabinets which cannot be reached by children should be encouraged.
5	60-61	Unclear meaning	To support the implementation of….. …….by stakeholders
5	62	Comma missing	errors, the
5	84	Duplication of the word in	remove 'in'
5	87-89	This (CQI) is not a term that is used in the Good Vigilance Practices and seems rather specific. It seems to there to make a point that it is important that medication errors are evaluated, corrective and preventative actions considered, proportionate to the risk and in accordance with quality management systems (which is also a requirement for the pharmacovigilance system).	Re-word and align with existing quality system concepts available in GVP
5	97	Missing reference to the separate guidance document	Include reference
5	153	Corrective measures are also important	Corrective and preventative measures
5	158-167	Is there clarity over whether medication error risks are considered in the definition of signals that exists in GVP? If so, then their tracking, evaluation and reporting will also be covered in the existing requirements.	Clarify whether medication error risk is considered to be included in the definition of a safety signal.
5	182-187	Is an unintended co-prescription with a concomitant medicine which is contraindicated due to interaction also a medication error?	Clarify.
5	275-276	Is an unintended co-prescription with a concomitant medicine which is contraindicated due to interaction also a medication error?	Clarify.
5	321	Incorrect use of word 'we'	S(he) was…
5	346	Unclear meaning 'concentration potassium'	Concentrations of, or concentrated ?
5	373	Missing comma	procedures, reached

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5	423-435	The ability to determine the cause of the error is dependent on the quality of the report received. In some instances it may not even be possible based on the level of information available.	It would be useful to indicate that individual cases of medication error should be properly followed-up in the first instance, in order to obtain an accurate version of events and factors contributing to the adverse event(s)
5	423-435	It is unrealistic for a full RCA to be performed for every individually reported medication error and seems to be introducing a new requirement for AE handling. Note that ICSRs should be accompanied by an assessment of causality.	Re-inforce the existing requirements for follow-up and causality assessment, indicating that RCA would be a necessary activity when determining what actions to take.
5	423-435	The focus should be on trending analyses etc. and the obligations already described in the processing and evaluation of ICSRs.	Possibly it is more appropriate to revert back to the analysis of reported events, and that signal investigation could include RCA
5	423-435	How would expectations differ for those medication errors that have resulted in an adverse event vs those where there was no associated AE.	Clarify expectations for medications errors with / without reported AEs and how a risk based approach to the level of investigation could be applied.
5	476	Erroneous inclusion of word 'by'….'with by'	Delete 'by'
5	760-762	That the pharmacovigilance provisions we have since 2012 have 'major' limitations - this would need qualifying. Routine pharmacovigilance does not only encompass spontaneous reporting.	This sentence needs to be clearer: if it is to mean that analysis of spontaneous reporting *alone* may be insufficient to anticipate, detect and manage medication error risk, then it is more acceptable. If it is to mean that further research may be needed to fully characterise medication errors (i.e. when and how medication they occur) and therefore other methods of monitoring should be considered, then it needs to state this
5	869-	Provisions also exist to provide patient information in alternative formats, when requested.	It would be useful here to refer to/ reinforce existing requirements for MAHs to provide alternative format patient information (Dir 2001/83)
5	884	Both the abbreviations PIL and PL have been used throughout the document.	Patient Information Leaflet (PIL) or Package Leaflet (PL) throughout.

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5	886-892	Existing guidance states that side effects should be listed by frequency and where frequency is unknown it should specify this.	Needs to be in line with the advice given in the QRD guidance (version 9, 03/2013) http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf
5	889	Random end bracket	Remove bracket
6	1122 – 1126	Santen welcomes the Agency's initiative in establishing a good practice guidance, which will substantially contribute to improve clarity and understanding of the nature and origins of medication errors. Annex 1 to the guidance (lines 1035 – 1200) describes 'Sources of medication error in medicinal product design'. The identified risks are classified by the pharmaceutical form and nature of the drug. Medication designs known for potential medication error are described in a general way, i.e. not indicating a specific medicinal product. This strategy is changed for topical products (lines 1122 - 1126), where specific product example is given to describe a risk known to be related to unit dose droppers in general. Santen agrees that the design of unit droppers is of ultimate importance to ensure safe application to the eye. However, Santen urges the Agency to abstain from a wording which misleads a general risk related to a pharmaceutical form to a specific medicinal product, which can be identified by the data provided in this section.	Eye drops are often presented in a bottle or individual single-use droppers but these can be difficult to hold and use for patients with manual dexterity problems. Related to this, single-use droppers which are broken open to use may leave sharp edges, which could damage the cornea ~~(e.g. as with timolol and dorzolamide eye drops after the introduction of a new design of dropper, reported in July 2013)~~.
7	734-737	EMA and the other national agencies in charge of medicines in Europe, including the ANSM in France, are already at fault for not having yet been able to impose to the pharmaceutical industry the presence of a bar code on each immediate container for every medication used in hospitals and nursing homes.	Rather than writing a "good practice guide on risk minimisation and prevention of medication errors", EMA, ANSM, and the other national agencies in Europe should better act to prevent the huge preventable, and set the minimal conditions required to implementing "closed loop medication administration" in the hospitals and nursing

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		Do we still have to wait another couple of months or years? Is the huge number of lives already estimated to have been saved from a preventable death linked to medication errors recorded in the United States of America in December 2014 by MEDICARE and the AHRQ still not enough to urge a move toward a feasible start of implementation of Bar-code medication verification at the bedside of European hospitalized patients? Barcode medication administration (BCMA) system was first developed in 1995, at the Veterans Affairs Medical Center in Topeka, Kansas, and was introduced nationwide in 2000[2]. Then, on the 25th of February 2004, the FDA Commissioner and US Health & Human Services Secretary announced new requirements for bar codes on drugs and blood to reduce risks of medication errors. By the 26th of April 2006 a bar-code was mandatory to appear on each immediate container of every medication to be used in hospitals [3, 4, 5, 6]. It was expected at the time of the announce that nearly 500,000 adverse drug events and transfusion errors would be prevented over 20 years as soon as the new bar-code rule would be fully implemented. Then, the Brigham and Women's Hospital in Boston, started in 2005 the pivotal study published in the New England Journal of Medicine the 6th of may 2010, that brings the	homes within the European community. That means these agencies have to whistle the end of the recess, and to oblige pharmaceutical industrials to put a datamatrix on each immediate container for every medication used in hospitals or nursing homes. The soonest will be the best to avoid thousands preventable deaths each year in Europe and hundreds of thousands adverse drug events from medication administration errors...

[2] Barcode Medication Administration: Lessons Learned from an Intensive Care Unit Implementation. Dans "Advances in Patient Safety: From Research to Implementation (Volume 3: Implementation Issues)", AHRQ, 02/2005. Access verified the 10-06-2015 : : http://www.ncbi.nlm.nih.gov/books/NBK20569/pdf/ch32.pdf
[3] Bar code label requirements - Code of Federal Regulations Title 21 Sec. 201.25 - Access here
[4] "The bar code must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act" - Access here ("The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article" ≠ outside container)
[5] Guidance for Industry - Bar Code Label Requirements - Questions and Answers - Draft Guidance - FDA 06/2005. Access here
[6] Guidance for Industry - Bar Code Label Requirements - Questions and Answers - FDA 08/2011 : here

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		best evidences of BCMA efficacy to prevent medication errors and linked adverse drug events [7]. The BCMA system enables nurse to check the "5 rights" of the patient: right patient, right route, right drug, right dose and right time. Furthermore, it makes available at the point of administration pertinent patient- and medication specific information and instructions entered into the pharmacy/hospital computer system and can prompt the nurse to record pertinent information before administration may be documented [8]. In 2012, there were already 11 prospective studies published to assess BCMA efficacy [9]. Pharmaceutical companies were prompt to comply with the new FDA requirements, and as soon as 2010, 88% of oral solid medications were available in unit doses to the North-American hospitals [10]. At the end of 2013, 80% of hospitals in the USA have already implemented BCMA [11]. Even better than BCMA for patient safety is the "Closed loop medication administration [12]". At the end of the first quarter of 2015, HIMSS Analytics scored 56.7% of 5,462 North-American hospitals already have implemented both BCMA and CPOE (computerized order entry) [13]. The 18th of December 2014, AHRQ published online on its	

[7] Effect of Bar-Code Technology on the Safety of Medication Administration. Eric G. Poon et al. N Engl J Med 2010;362:1698-707. Open access here.
[8] Medication Safety Report, Creation of a better medication safety culture in Europe: Building up safe medication practices; Council of Europe, Mars 2007. Access here.
[9] Effects of bar code-assisted medication administration (BCMA) on frequency, type and severity of medication administration errors: a review of the literature. J. Hassink et al. European Journal of Hospital Pharmacy 2012; 19: 489–494. Access here.
[10] Unit Dose vs. Bulk Oral Solid Medication Purchasing Patterns and Repackaging: Sampling and Analysis. White Paper. McKesson. 2010. Access here
[11] ASHP national survey of pharmacy practice in hospital settings: Prescribing and transcribing - 2013. Craig A. PEDERSEN et al. Am J Health-Syst Pharm. 2014; 71: 924-942. Access to abstract here.
[12] "The closed loop medication administration with bar coded unit dose medications environment is fully implemented. The eMAR and bar coding or other auto identification technology, such as radio frequency identification (RFID), are implemented and integrated with CPOE and pharmacy to maximize point of care patient safety processes for medication administration. The "five rights" of medication administration are verified at the bedside with scanning of the bar code on the unit does medication and the patient ID". See Electronic Medical Record Adoption Model (EMRAM) stage criteria: here.
[13] EMRAM : here.

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		website very impressive results on outcome [14]. The achievement of targeted meaningful use in the US hospitals, namely "closed loop medication administration" and "medication reconciliation", is accompanied by a dramatic reduction in deaths related to medication errors with 11,540 deaths averted over the period 2011, 2012 and 2013 compared to 2010, including an estimation of no less than 6,020 prevented deaths in 2013, and 577,000 adverse drug events related to medication errors would have been avoided over the same period, of which 301,000 ADE averted solely in 2013. Far from the good practices being implemented in the US, the situation is catastrophic in Europe, and particularly in France. Only 44 to 47% of oral solid medicines are presented in unit doses still identifiable until the very moment of their administration [15, 16, 17]. Even worse is the actual presence of bar-codes on the immediate container of hospital medicines. Among 572 presentations of medications, from all types of pharmaceutical forms, evaluated in a French hospital, only 21% had a datamatrix, and only 12% a datamatrix scannable [18]. Despite iterative request from the European Association of Hospital Pharmacist [19], agencies	

[14] Interim Update on 2013 Annual Hospital-Acquired Condition Rate and Estimates of Cost Savings and Deaths Averted From 2010 to 2013. Access: here.
[15] T'as le look coco - Ressemblances (look-alike) des formes orales sèches, l'expérience d'un centre hospitalier. Poster de l'équipe de M. Claude DEMANGE, CH ST-DIE-DES-VOSGES présenté aux rencontres 2014 de la revue Prescrire. Catégorie « Eviter l'évitable ». Open access here.
[16] Démarche d'amélioration de la prise en charge médicamenteuse du patient en Unité de Soins de Longue Durée (USLD). PUI/USLD/EHPAD CH FIRMINY. Poster N°31, présenté à HOPIPHARM 2013, Lyon. Access: here.
[17] Médicaments à risque : focus sur la présentation unitaire des médicaments. PUI CH SECLIN. Poster N°38, présenté à HOPIPHARM 2014, La Rochelle. Access: here.
[18] Sécurisation du circuit du médicament par l'utilisation des codes à barres standardisés. Georges NICOLAOS et al., CH Coulommiers, GH Est-Francilien. Poster I159 présenté au Congrès « Rencontres CSH 2013 », Marseille, septembre 2013. Access : here
[19] Request for the production of single dose-packed drugs, EAHP, 06/2007, revised 06/2010: here

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		and political deciders remained deaf. Paradoxally, a single decision [20] from the director of AFSSAPS (previous name of ANSM, our national agency in France, was sufficient to obtain industrial compliance to put a datamatrix on each medicine box (outside or secondary container). In February 2014, 99,3% of medications available in the 28 hospitals of Assistance Publique - Hôpitaux de Paris had a datamatrix on the outside container [21].	
8	147	First use of the abbreviation 'RMP' therefore needs to be defined.	The risk-management plan (RMP) should be used to document the safety considerations…
8	793-841	Some liquid oral medicinal products are available in multiple strengths. This can lead to confusion and risk of wrong product selection by the prescriber or during the dispensing process. This is a particular issue when the different strengths are have a similar appearance or are presented in similar packaging. There is also potential for confusion for parents or carers if they are given a different strength of liquid oral medicine to that usually obtained.	
8	793-841	Prescribers should be encouraged to prescribe liquid oral medicines for children with doses in weight (e.g. milligrams) rather than volumes (e.g. millilitres). This is especially important where products are available in multiple strengths.	
8	1078-1086	Patients may take the wrong dose in situations where multiple liquid medicine strengths are available but presented in similar packaging and have a very similar appearance in terms of colour, size and flavour.	
10	1292	Suggestion for addition to the paragraph on Products for IV use or	

[20] Avis aux titulaires d'autorisation de mise sur le marché de médicaments à usage humain et aux pharmaciens responsables des établissements pharmaceutiques mentionnés à l'article R. 5124-2 CSP. J. MARIMBERT, Directeur Général, AFSSAPS. Texte 107 sur 131. JO du 16 mars 2007. Access here.
[21] Bilan de l'utilisation du Datamatrix lors de la préparation des produits de santé. AGEPS, Service Approvisionnement Distribution. Poster N°184, présenté à HOPIPHARM 2014, La Rochelle. Access : here.

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		parenteral administration: Instructions for calculating when robots are dispensing should be part of SPC. This has to do with how the whole bottle content is expressed – is it the actual content or is it the content that can be extracted from the bottle (assuming some medication is left behind). In Denmark for instance, this has caused a major incident.	
10	1307	Educational material and/or SPC should, when relevant, include calculation tablets in which dose is calculated from mg per weight or per Body surface or per renal function into actual dose. This is particularly relevant for paediatrics and for orphan drugs.	
10	1203 (Annex 2)	The following information could be added: - Numbers like 12,5 mg vs 125 mg 1 mg vs 10 mg, 2 mg vs 20 mg, can easily be mixed up. Suggestion to use numbers that differ more, i.e. 3 mg vs 20 mg, 2 mg vs 10 mg etc. - Establish agreement among companies on colour coding for particular forms or medications dealing with the same disease – for the safety of the patient. - Point out clearly in the SPC when particular errors are known to have caused serious harm. For instance methotrexate causes serious harm if given daily for two weeks.	
11	11-16	As part of the public consultation of the draft good practice guide on risk minimisation and prevention of medication errors the European Medicines Agency (EMA) would also like to take the opportunity to obtain stakeholder feed-back on the following questions: 1. With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in harm during the post-authorisation	

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		phase useful taking into account the regulatory remit for risk minimisation measures? We welcome the inclusion of examples into the guideline. These are most helpful.	
11	84	In ~~in~~ most cases medication errors are preventable, provided that the potential….	Double 'in'
11	159-160	…may be in place ~~in place~~ to reduce the risk of medication error.	Double 'in place'
11	459-461 1295-1296	"It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or care givers or whether more prominent warnings should be included on the packaging so that these are not overlooked… Products which require dilution should have this clearly marked on the immediate label along with any incompatibilities."	Care should be taken that this example is very special. It should be avoided to establish the general use of warnings on the outer packaging since this could 'teach' HCPs not to read the SmPC anymore. We suggest to restrict this requirement to very distinctive cases.
11	521	Brand names	To point out the responsibility of other departments than PHV (e.g. Legal, Regulatory Affairs, Marketing, etc.) we strongly recommend to extend and amend Chapter 6.6.2.1. of the 'Guideline on the acceptability of names for human medicinal products processed through the centralised procedure' with this information regarding the context of medication errors and brand names.
11	554	…excipients, method/rout of administration…	'route'
11	723-724	The inclusion of the following in this guidance in intended only to raise awareness of those tools…	The inclusion of the following in this guidance is intended only to raise awareness of those tools…
11	799	Manias et al 201324	Manias et al 2013[24]
11	859-860	It is important the appropriate materials for elderly patients are	It is important that appropriate materials for elderly

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		developed and user-tested, including use of large print text and Braille for patients with impaired eye sight	patients are developed and user-tested, including use of large print text and Braille for patients with impaired eye sight.
11	903-905	It is also important to consider communication on medicines safety for HCPs. This is largely based on information presented in the SmPC, but these documents can be lengthy and they are not always consulted.	It would be important to emphasize the importance of the SmPC in the guideline instead of explaining why it is not often consulted. The quality and format of the SmPC should be further improved.
11	1193	…recommended by the manufacture	recommended by the manufacturer
11	1304-1306	Information on the appropriate dilution of solutions should be included in the SmPC and products requiring dilution require a Technical Information Leaflet (TIL) for use by HCPs to accompany the PIL; information on dilution should be described in the TIL.	Information on the appropriate dilution of solutions should be included in the SmPC and products requiring dilution require a Technical Information Leaflet (TIL) for use by HCPs to accompany the PIL; information on dilution should be described in the TIL (if applicable).
12	92	"… in relation to medication errors arising from the medicinal product…" Are cosmetics and food supplements also concerned?	
12	135	"whether any significance changes"	"whether any significant changes"
12	191-195	Mention of the study does not add any value to the topic. The guide should focus on guidance and concept.	Subjects in clinical trials are typically closely monitored and have at least semi-regular contact with study investigators during the trial. This controlled environment may therefore not reflect 'real world use', but even in the clinical trial scenario, medication errors may still occur. ~~One study5 of cancer clinical trials suggested the most common type of errors were prescribing (66%), improper dose (42%), and omission errors (9%). The study found that not following an institutional procedure or the protocol was the primary~~

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			~~cause for these errors (39%), followed by the written order (30%), and poor communication involving both the healthcare team and the patient (26%).~~
12	281	Add a bullet point to improve readability	Medicinal products may not be down-titrated appropriately: • a patient developed 'grey man syndrome' when prescribed amiodarone 200mg three times daily for a month instead of being down-titrated to 281 200mg daily after a week. In some situations the periodicity of dosing may differ across various indications, e.g.: • …
12	361-374	We recommend to add bullet points for better readability	• A product presented as two ampoules (one containing water as the solution for injection and another containing the powder for solution) was labelled only with the trade name. This introduced the 362 possibility for misunderstanding, because the ampoule with the solution may be mistaken for the medicinal product containing the active substance and the patients may receive only water for injections. The product was relabelled to make it clear that the ampoule containing a solution contained water for injection, for use with the active substance. • Treatments given by the intravenous (IV) route are associated with the highest rates of preparation and administration error due to issues such as incompatibility with diluents or by injecting bolus doses faster than the recommended slower infusion

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			time. • Medicinal products for IV use may be inadvertently given by the subcutaneous (SC), intradermal or intra-muscular (IM) route rather than by infusion. • Cases of needle contamination can also result in accidental exposure to product or exposure to contaminated device (e.g. a case of adhesive arachnoiditis and paraplegia was reported when chlorhexidine, used as topical disinfectant in epidural or spinal anaesthesia procedures reached the meninges via a contaminated spinal/epidural needle).
12	36	Medication error assessment following the identification of the problem, causes of the problem and identification of solutions is difficult to apply for non-prescription medicines (see general comment above).	
12	445-484	Copy/paste of GVP Module XVI. We would suggest summarising the most important concept and referring to the GVP Module.	Risk minimisation activities can mitigate the risk of medication error related to the medicinal product. This guidance is complimentary to the recommendations in Good Vigilance Practice Modules V12 (Risk management) and XVI13 (Risk minimisation measures: selection of tools and effectiveness) which offer guidance on the development of risk minimisation tools. ***Example of*** *routine risk minimisation:* ~~Routine risk minimisation measures apply to all products and include:~~ ~~• the summary of product characteristics;~~

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			~~• the labelling;~~ ~~• the package leaflet;~~ ~~• the pack size(s);~~ ~~• the legal status of the product.~~ Pack size limitations can reduce the risk of medication errors in the form of patients taking too many tablets (leading to overdose) and require the patient to return to the prescriber, who can check the status and progress of the patient and that the medicine is being used correctly. It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or care givers or whether more prominent warnings should be included on the packaging so that these are not overlooked (e.g. the labels for generic piperacillin/tazobactam carry a statement that they must not be mixed or co-administered with any aminoglycoside, and must not be reconstituted or diluted with lactated Ringer's (Hartmann's) solution; a similar warning is not required for the branded product as this has been reformulated to remove these incompatibilities). *Additional risk minimisation* ~~Additional risk minimisation measures may also be necessary in some circumstances and these encompass any measures beyond labelling, pack size and legal status.~~ ~~Additional risk minimisation measures should focus on the~~

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			~~prevention of medication errors, but the burden of imposing such measures on patients, HCPs and the healthcare system should be balanced against the benefits.~~ The most common form of additional risk minimisation is educational materials for HCPs and patients, but other approaches may also be considered in agreement with National Competent Authorities (e.g. educational videos showing correct reconstitution and injection of a solution, prescriber's checklists to ensure that appropriate pre-treatment tests have been performed, demo-kits for complex devices). Educational materials are predominantly paper-based but as risk minimisation evolves it is likely that MAHs will consider supplementing such materials with by internet-based activities and new technologies in prescribing and dispensing systems to improve safe medication practice, such as smart phone apps, bar–coding and pill identifier websites. This should be discussed and agreed with national competent authorities in all cases with input sought from the Working Group on Quality Review of Documents as necessary.
12	554	"method/rout of administration"	"method/route of administration"
12	1036 (Annex 1) 1203 (Annex 2)	There are other risks of medication error, including the confusion of a medical device with a medicine. Indeed, this confusion is about the similarity of the pharmaceutical form: the unit dose form. The most common example is the confusion of saline doses with doses of chlorhexidine or hydrogen peroxide. Risk minimisation measures are proposed in Annex 2	Addition of the following: In Annex 1: *"Different types of products can be presented as single dose (saline, chlorhexidine, hydrogen peroxide ...), which may well cause confusion. This source of error can cause*

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			side effects that can sometimes be serious. *These cases are predominantly present in the paediatric population, particularly in patients' homes. The confusion between ocular or nasal wash solutions with an antiseptic solution can have as consequences, especially in infants, respiratory failure."* in Annex 2: *"Single dose* *To minimise confusion errors, marketing authorisation holders may propose:* • *Changes of labelling,* • *Changes in the shape of the packaging,* • *Opacification or colouring of the packaging,* • *The ability to colour the solutions."*
13	158	Not clear what "When a potential risk of medication error" refers to. Does it refer to the risk of occurrence of the medication error or to the risk associated with this medication error? Not all identified medication errors have to be considered as an important risk in the RMP. The decision for classifying a medication error as an important risk should depend on the number of cases reported in clinical trials or in post marketing and also to the level of risk associated to this error (e.g a medication error whom the occurrence may lead to a risk having an impact on the risk-benefit balance of the product or have implications for public health)	
13	159-160		may be **put** in place to reduce the risk of medication error.

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13	160-162	Please clarify what "potential medication errors" refers to and confirm that it must be described in PSUR	Furthermore, MAHs have an obligation to describe and discuss patterns of medication errors ~~**and potential medication errors**~~ within every Periodic Safety Update Report (PSUR), even when these are not associated with adverse reactions.
13	162-166	Medication errors may occur in specific regions or countries due to local practices (e.g for vaccines where several parameters may vary from one country to the other: local vaccination schedules, HCP in charge of vaccination (GPs or nurses…), channels of distribution (GP's office, hospital, pharmacies)	The context of product use, including the setting, stage of medication process, category (type) of medication error, contributing factor(s), medicinal product(s) involved, **region/country of occurrence,** covariates defining the treated population, patient outcome, seriousness, mitigating factors and ameliorating factors should be considered and discussed in relation to these reports.
13	424	Why do we consider only serious adverse events? For example, medication error potentially resulting in lack of efficacy (without AE at time of reporting) may have serious consequences occurring several months or years after the error has been done. For example, use of a vaccine that was not correctly stored may lead to lack of efficacy and occurrence of a serious diseases later on.	The root cause analysis (RCA) is a structured method used to analyse serious adverse events **or potential serious adverse events or consequences** derived from errors.
13	466-484	Medication errors may occur in specific regions or countries due to local practices (e.g for vaccines where several parameters may vary from one country to the other: local vaccination schedules, HCP in charge of vaccination (GPs or nurses…dispensing and storage). In consequence, this may be relevant to put in place a risk minimisation measure only in a specific country?	Suggestion to indicate somewhere in the section that additional risk minimisation measures may be put in place locally. And clarify if this has to be described in the EU RMP in this case.
13	499-544	For vaccines, a common name is used as there is no INN. A specific section regarding the common names for vaccines should be added before the section "*Brand name*".	For vaccines, the common name is based on the title of European Pharmacopoeia monograph when one exists. Common names for new vaccines should provide the appropriate information to facilitate the identification of the

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			vaccine by the HCPs.
13	574-576	Revaxis is diphtheria, tetanus and inactivated polio vaccine (dT/IPV) and Repevax is a diphtheria, tetanus, inactivated polio and acellular pertussis vaccine (dTaP/IPV). When an adolescent is given Repevax instead of Revaxis, he will have received the intended diphtheria, tetanus and polio antigen to complete their childhood immunisation schedule.	Patients were mistakenly vaccinated with Repevax instead of Revaxis due to similarity in names, labelling and packaging; children over 10 years of age and unvaccinated children did ~~**not**~~ receive ***a dose of pertussis in addition to*** the appropriate booster immunisation against diphtheria, tetanus and poliomyelitis ~~**with Revaxis**~~.
13	615	After line 615:	For vaccines the common names can be very long and not be an appropriate information to facilitate the identification of the vaccine in the refrigerator. It may be preferable that the smaller faces of the carton box contains only the trade name, or the trade name and an abbreviation of the common name such as DTaP-IPV-HB-Hib, instead of the trade name and the common name.
14	262 ff	Three main sources of potential harm are outlined: errors in prescribing, dispensing and preparation / administration. What is missing here and should be addressed is the problem of omitting safeguards (e.g. taking PPIs in order to avoid NSAID-related GI bleeding, checking transaminases in order to timely detect ADRs of the liver during treatment with potentially hepatotoxic drugs). In addition, the steps of transcription and monitoring of the medication process should be mentioned.	
14	423-442	Since root cause analysis (RCA) is the method of choice for the assessment of causality and preventability of medication errors (MEs) it is appreciated that a section is devoted to that subject. However, this section is too short and superficial in that it leaves out fundamental aspects of RCAs and does not provide relevant	

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		literature for that. For instance, the concept of safety barriers and failures (e.g. Reason's Swiss Cheese model) as well as that of primary and secondary (and possibly tertiary) reasons of failure (e.g. Ishikawa's fishbone diagram) should be addressed.	
14	431	The statement 'A RCA should be conducted for any medication errors detected in the post-marketing environment' seems unfeasible, because a properly conducted RCA may well require several weeks of work at the site of the occurrence of the error. A restricted and well-targeted definition of the exceptional cases where a RCA seems necessary should be developed and included in the guideline.	
14	131, 340	'Lack of efficacy' should be replaced by 'lack of effectiveness', because it is used in the context of post-marketing real life treatment (rather than in controlled clinical trials).	
14	816-820	The situation has improved with the introduction of the paediatric regulation in 2006 (Regulation (EC) No 1901/2006) that places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. However, the ongoing limited availability of paediatric formulations may lead to misuse of product formulated for adults.	The situation has improved with the introduction of the paediatric regulation in 2006 (Regulation (EC) No 1901/2006) that places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. **PLEASE ADD: The Paediatric use marketing authorisation (PUMA) intended to bring approved drugs for adults to an exclusive use in children with age-appropriate formulation has not met expectations. Particularly,** the ongoing limited availability of paediatric formulations may lead to misuse of product formulated for adults.

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16	1114-1117	Under Implants, insertion of the device in the wrong place is listed and dexamethasone eye implant misplacement is given as an example for this medication error. The ECI-EEIG considers it unnecessary to refer to dexamethasone in this case since misplacing an eye implant may happen irrespective of the active ingredient contained in it.	*Implants* Some products are implanted into the body (e.g. contraceptive implants for insulin infusion pumps) and there may be errors associated with the insertion of the device or its removal, insertion in the wrong place (e.g. eye implant misplacement), devices moving or breaking internally (and perforating tissues), or becoming difficult to locate.
16	1122-1126	Under *Topical products*, reference is made to the design of single-use droppers for eye drops that impose a risk when they leave sharp edges after breaking off the tip for use. This is a general and well-known risk related to this particular pharmaceutical form. Therefore, while the example reported in July 2013 is a valid case, it is not justified to cite a specific medicinal product by mentioning the active ingredients and the date when this was reported.	Eye drops are often presented in a bottle or individual single-use droppers but these can be difficult to hold and use for patients with manual dexterity problems. Related to this, single-use droppers which are broken open to use may leave sharp edges, which could damage the cornea.
16	1127-1129	The average volume of a drop dispensed from an eye drop bottle is in the order of 30µl. While the volume of the conjunctival sac is significantly smaller than this amount, 15 – 20µl rinse out of the eye and have to be removed e. g. by wiping off with a tissue. Therefore, while larger drop sizes or the administration of more than one drop upon squeezing the eye drop bottle may be a risk for the surrounding skin of the eye, it is not a matter of overdose. An overdose would be instilled if several drops are administered in intervals of several (five or more) minutes.	For drops presented in larger bottles, instructions for use vary and patients may squeeze the bottle excessively, thereby delivering a larger amount of solution which could have a noxious effect on the surrounding skin of the eye.
17		There is a discrepancy in respect of the omission error between the documents. In contrast to the "*Good practice guide on recording, coding, reporting and assessment of medication errors*" the omission error is here often mentioned, e.g. on page 22: omission	

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		errors occur with 11,8 % under the most common types of prescribing errors. This conflict should be taken into account. In our point of view it would be useful to harmonise these documents.	
17	1152	There are also problems if the strength data on ampoule labels is given as a concentration, e.g. in mg/ml but the real content of active substance is much higher (or less). If the medicine is used without recalculation or reading the label text with the real content carefully, an overdosing (under-dosing) is unavoidable.	
17	1171	a.) Two medicinal products with the same active substance are identical in the concentration of the active substance (e.g. 17 mg/g), but the drop devices produce various drops in size or weight. Therefore the amounts of the active substances differ and must be recalculated before use. Otherwise an over- or under-dosing result. b.) Different pack sizes are available with different drug devices (e.g. dropping bottle with 30 ml solution and a 100 ml bottle with an oral syringe). Although the kind of administration have to be changed the 100 ml bottle is mistakenly further dropped. This handling lead to dosing problems with resulting over- or under-dosing.	
18	308	"U" as an abbreviation for units is sometimes also written as "iu" for international units – the "i" can be read as a "1" so 5 iu has been interpreted as 51 units.	Add this as another example.
18	383	Another example of omission of a medicine was when a hospital in-patient's dose of levetiracetam was delayed because the company name was included as part of the drug name all on one line, and the hospital staff were unsure what the significance of this was and	Appreciate this may be related to EMA licensing requirements, but the way the text was arranged spatially on the box did lead to confusion.

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		whether it was “normal” levetiracetam and not some unusual formulation.	This is linked to document line 538 and the EMA’s Name Review Group – when the company name is part of the drug name, can the format/layout of the text be considered too?
18	394	The document gives that product information for all medicinal products should carry a contra-indication for use in patients with known hypersensitivity to the active ingredient or excipients. This information is given in the PIL, and sometimes on the outer box/primary packaging.	It would be of benefit to patient safety if this warning was always present on the box/label. Eg. penicillin containing products, especially vials which are presented in boxes of 10 with only one package insert. If this is removed and not replaced after use there may be no other obvious means of identifying the product as a penicillin if there is no warning on the box/vial labels. Ideally all penicillin containing products (including oral products) should have “contains penicillin” on the outer packaging/label from a patient safety angle. This is linked to document line 459 which considers whether critical information provided in the SmPC or PIL is likely (or able) to be read by HCPs.
18	1130	Aerosols: some nebuliser solutions are presented in individual dose plastic containers. These may be described as “nebules” on the packaging, but some are described as “ampoules” for inhalation use. This later description may lead to inappropriate administration as ampoules are generally regarded as containing medicines for injection.	Include statement that extra care should therefore be taken with such products.
18	1139	As well as a number of inhaler devices, there are also a number of spacer devices. Some of these do not physically “fit” all of the inhaler combinations that a patient might be using. This may lead to the need for patients to carry more than 1 spacer device with	Add a sentence to the effect that there are a range of inhaler spacer devices available, and that not all are compatible with all inhalers and that they may not be interchangeable.

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		them (some patients have been known to “make” one spacer device fit all their inhalers, or remove cannisters from one inhaler actuator to another while taking a dose). Also, if a patient’s brand of inhaler is changed this may necessitate a change in spacer device – if a routine prescription the patient may not immediately realise their new inhaler would not fit.	
18	1156	The example mentions 5% dextrose USP – the SmPC gives this as 5% glucose	Change the text to give 5% glucose
18	1307	There is no mention of the importance of tamper evidence.	Consideration of tamper evident features eg. on emergency use pre-filled syringes, tubes/tubs of creams and ointments, inhaler boxes, mouthwashes. Tamper evidence may help to reduce errors of administering a product to more than 1 patient, or incorrect administration if a medicine were taken out of its box, not then used, and replaced in the wrong box.
19	158	As there for all medicinal products will be a potential for medication errors, it is important to specify that it is only those medication errors considered an **important** safety concern that should be captured as important ris	When an important potential risk of medication error has been identified, medication error should be captured in the RMP as an important risk and both routine and additional risk minimisation measures may be in place in place to reduce the risk of medication error.
20	71	Add “preparation for administration” in this section	“(…) including the prescribing, dispensing, *preparation for administration,* or administration of a medicinal product (…)”
20	84	Duplication of ‘in’	Proposal to remove the duplicated ‘in’
20	84-86	Lines 84 – 86 state “in most cases medication errors are preventable, provided that the potential risks of medication errors have been considered during the product development and early	Revise the paragraph as follows (see the underlined and strikethrough portions):

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		marketing phases (when most medication errors will occur)…" It is not reasonable to assume that most medication errors will occur at early marketing phases. Rationale: The existing text suggests that most medication errors will occur at the early marketing phase of the medicinal products, which is misleading. The intent of the risk management plan is to minimize medication errors proactively. This is clearly stated section 2.0 (scope) where the EMA states, "…the measures implemented to minimise the risk of these occurring and suggests proactive approaches to risk management planning throughout the product life cycle".	*In most cases medication errors are preventable, provided that the potential risks of medication errors have been considered during the product development ~~and early marketing phases (when most medication errors will occur)~~ and evaluated throughout the product lifecycle.*
20	92	Include delivery system under scope. Rationale: Delivery system is not identified.	Recommend revising the paragraph as follows (see the underlined portions): *…from the Medicinal product and its delivery system (if applicable)…*
20	127-128	The list of stages where medication errors can occur in this line includes 'provision of information'. This is the first time a stage of provision of information has been included in the list of stages when a medication error can occur. Suggest deleting for consistency with rest of this document and other guidance.	'Medication errors can arise at any stage of treatment process, including prescribing, dispensing, preparation for administration, and administration ~~and provision of information~~. Such errors …'.
20	126-127	Specify also that the medicinal interactions with the development of new products (which could be used with the concerned product) and the new modalities of treatment/clinical practice should be taken into account for the potential medication errors, in addition to the product development process	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
20	129	Population is added after patient, but it seems this is more relevant to individual patients.	'…of administration or administration to the wrong patient(s)~~population~~. The consequences may include…'
20	145-146	Add to be careful to differentiate the packaging when several dosages of a product are available.	
20	158-159	This states that if a potential risk is identified around a medication error, it is an 'important' risk. Please delete 'important'; not all risks associated with medication errors will meet the definition of an important risk.	'When a potential risk of medication error has been identified, medication error should be captured in the RMP as a ~~an important~~ risk and both routine and additional risk minimisation measures may be in place in place to reduce the risk of medication error'
20	158-159	The proposed text states that when a potential risk of medication error has been identified, it will be included in the RMP as a potential identified risk. The potential for medication error is included in the RMP but only infrequently as an identified or potential risk. The proposed wording can be interpreted such that the potential for medication error would be included as a potential risk in the RMP almost routinely. Is this intended?	Additional guidance required relating to the conditions in which the potential for medication error should be included as a potential risk.
20	160	Typo error: "in place" written twice	
20	170	Many medication errors arise as a result of errors of prescribing by the health care practitioner. How much of the consequent health care burden is actually preventable by risk management measures implemented by MAH?	Distinguish between medications errors arising through poor medical practice and those arising as a result of preventable actions (to be implemented by the MAH)?
20	178	FDA reference to medication error document does not work.	Replace foot note link with "http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf"
20	184-185	"This requires an overview of available treatment options at the EU Member State level."	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		There are practical difficulties in getting an overview on packaging information/product design of available treatment option at the EU level from different manufacturers (prescription medicine). How shall this be practically implemented?	
20	186	"Confusion of mix-ups between products with the same indications due to similarities in posology" Mix-ups are not limited within the same indication, but can occur also between different indications and therapeutic areas.	Delete 'with the same indications'
20	182-184	The word "armamentarium" is not commonly used, suggest changing this to something more readily understood by the wider audience	Heading: *Medication Errors in the context of the available range of therapies ~~therapeutic armamentarium~~ .* It is important to explore the potential for medication errors in the context of the available therapies ~~therapeutic armamentarium~~ and where a new product may sit within this collection.
20	198-206	Lines 198 – 200 state that *"However, the clinical trial setting may be particularly useful for identifying any difficulties using medicines presented with a device or as a premixed solution for administration. This may allow for an early indicator of refinements that may need to be made to the design of the product or instructions for use prior to labelling, approval and marketing. During clinical trials, it may become evident that some drug product design features increase the risk of medication errors. In this scenario, Applications should provide an appropriate risk analysis for medical errors detected in the clinical trial programme and use this as a basis for refinement in the proposed pharmacovigilance and risk minimisation activities (or both)". We*	Revise the paragraphs as follows (see the underlined and strikethrough portions): *~~However, the clinical trial setting may be particularly useful for identifying any difficulties using medicines presented with a device or as a premixed solution for administration.~~ Usability study and clinical study have different objectives. Inclusion of a usability study in a clinical trial setting is not recommended. Simulated use testing conducted with representative users under reasonably realistic use condition is generally sufficient to evaluate use-related risks. Simulated use study ~~This may~~ allows for an early indicator of refinements that may need to be made to the

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		recommend that the EMA clarifies that a clinical trial is designed to evaluate clinical endpoints. A usability study is not a clinical trial and should be conducted outside the clinical trial setting. Rationale: A clinical trial is designed to assess clinical endpoints, which are distinctly different to usability objectives. Clinical study design to assess usability must allow for use errors. Use errors may confound clinical data or pose ethical issues. Therefore, usability studies should not be part of clinical studies.	*design of the product or instructions for use prior to labelling, approval and marketing. However, in cases where the type of delivery device or use environment are complex and the use conditions are not well understood, it might be necessary to validate a device under conditions of actual use. Actual use study, if conducted, shall be observed and assessed by a human factor expert.* *During clinical trials, clinical complaints or use related adverse events may be collected to further understand the potential use-related errors ~~it may become evident that some drug product design features increase the risk of medication errors~~. In this scenario, Applications should provide an appropriate risk analysis for medical errors detected in the clinical trial programme and use this as a basis for refinement in the proposed pharmacovigilance and risk minimisation activities (or both).*
20	188-189	It would be helpful to reword the text on contact for clarity.	Subjects in clinical trials are typically closely monitored and have ~~at least semi-regular~~ contact with study investigators during the trial at a frequency defined in a protocol. This controlled environment may therefore not reflect 'real world
20	207-208	The title of section 5.2.3 (Data from "failure mode and effects analysis" and "human factor testing" (pre-authorisation)" is misleading and does not align with the contents of the paragraph. Rationale: "Failure modes and effects analysis" is a specific risk assessment technique, and "human factors testing" is a facility of a technique to assess usability. Human Factors testing provides input	Revise the title of the paragraph as follows: *Use related risk analysis and Human Factor/Usability Engineering*

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		to inform risk analysis.	
20	209	Risk management is stated in this paragraph; however the topic of risk management is not adequately described. Rationale: Description of the risk management topic is recommended to ensure clarity between risk management and human factor testing.	Revise the paragraph as follows (see the underlined and strikethrough portions): ~~*Successful risk management is based, in part, on effective quality management systems and a number of tools may be useful in proactively identifying and assessing the risk of medication errors".*~~ *Risk management is an important part of the development of medicinal products with delivery systems. Risk management involves systematic application of policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.*
20	211-216	Should this proposal be included in specific development guidance? Description of problems that have occurred in development e.g. in RMP or periodic report is post hoc observation and too late for effective prevention.	Formalise requirements for design testing as routine part of development processes.
20	214-216	Perception-Cognition-Action (PCA) Analysis is an approach to the broader activities of "Task Analysis". Rationale: Many equally effective methods are possible for medicinal products and no one method should be suggested. More commonly used methods are: "Cognitive walkthrough" and "Heuristic Evaluation".	Revise the paragraph as follows : *The report of the EMA's 2013 workshop on medication errors notes the Pharmaceutical Industry's suggestion to use other methods of human factor engineering to inspect the usability of the product* ~~*that test how the actual product is used*~~*, including cognitive walkthrough, heuristic evaluation and task analysis methods such as the "perception-cognition-action" (PCA) analysis, to be carried out early in development.*
20	220	The guidance should recommend use of the harmonised EN 14971 as the risk management standard; however the guidance should not dictate the specific risk management tool to be used.	Remove section 5.2.3.1 from the guidance. Reference to EN ISO 14971 has been stated in the draft guidance.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		Rationale: EN ISO 14971 utilizes systematic application of management policies, procedures, and practices to the takes of analysing, evaluating, and controlling risk. Compliance to this standard is sufficient to assure the safety of the medicinal products. Other than FMEA (as suggested in the draft guidance), there are other risk management tools such as Fault-Tree-Analysis and Hazard Analysis that are equally effective in management risks. Roche believes that the guidance should allow flexibility for the manufacturer to select the appropriate risk management tools to be used.	
20	231	The title of section 5.2.3.2 “Simulated use testing” is misleading. Rationale: The contents of the paragraph describe the legal basis associated with the usability testing; however not all usability testing is simulated use.	Revise the title of the paragraph as follows: *5.2.3.2. ~~Simulated use testing~~ Human Factors Testing*
20	232-233	The line “there is currently no legal requirement for user-testing of instructions for use or administration or…” is not accurate and discourages sponsors from performing user testing. Rationale: The statement “there is currently no legal requirement” is not accurate. For medicinal products delivered via a delivery device, compliance to the Annex I of Medical Device Directive applies (93/42/EEC) is required. Harmonised standards requires provision of objective evidence the resulting product is capable of meeting the requirements for the specified application or intended use (ISO13485:2012- part 7.3.6) and can be used safely (IEC62366:2015-part 3.13). User testing is a commonly used	Revise the paragraph as follows: *~~There is currently no legal requirement for user-testing of instructions for use or administration or reconstitution of medicines in order to investigate the potential for medication errors~~ For medicinal product delivered using an non-reusable, single unit integrated medicinal product with delivery device, compliance to the Annex I of the Medical Device Directive (93/42/EEC) is required to assure the safety and performance of the device. The following EU harmonised standards can be used to demonstrate compliance of use safety requirements of the Annex I: (1) EN ISO 14971:2012 - Risk Management, (2) EN ISO*

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		method of meeting this requirement. For medicinal products not associated with a delivery device, these requirements do not apply.	*13485:2012 – Quality Management System, specifically section 7.3.6 (Design and Development Validation), and (3) IEC 62633:2015 – Application of Usability Engineering to Medication Devices. For medicinal product not associated with a delivery device, Annex I requirements do not apply*.
20	231-236	Use testing section is not sufficiently informative. Rationale: It would be beneficial for the EMA to strengthen the guidance on performance of simulated use testing to better serve the needs of the EMA and Industry.	Add the following paragraph in section 5.2.3.2: *User testing may be performed throughout the device and labelling material development process to identify the end-user needs and inform the design and development. User testing also helps to identify potential use-related hazards of the device and its context of use to inform the overall use related risk management process. Ultimately user testing can also be used to validate safe and effective use by intended users. When performing user testing sponsors should consider testing the intended use of the product with a range of representative end users, under representative use environments and use scenarios.*
20	238-239	Lines 238 – 239 state "for medicinal products delivered via device, the International Standard (ISO14971:2007 Medical Devices – Application of Risk Management to Medical Devices) should be followed". State that EU harmonised standard for risk management (EN ISO 14971:2012) should be used to demonstrate compliance with the Annex I of the Medical Device Directive (MDD) (93/42/EEC[22]). EN ISO 13485:2012 should be referenced. The statement that describes ISO 14971 as a recognized consensus standard would be better positioned in the section where risk	Revise the paragraph as follows : *For medicinal products delivered via a delivery device, the EU harmonised ~~International~~ standard (currently: EN ISO 14971:~~2007~~ 2012 Medical Devices – Application of Risk Management to Medical Devices and EN ISO 13485:2012 – Quality Management System) should be followed.*

[22] 93/42/EEC amended by 2007/47/EC, hereinafter referred as to "93/42/EEC".

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		management is introduced (section 5.2.3, lines 209-219). Rationale: The current EU harmonised standard for Risk Management (EN ISO 14971:2012) is needed to demonstrate compliance with the MDD Annex I requirements (safety and performance) for medicinal product delivered with a delivery device. EN ISO 14971:2012 differs from ISO 14971:2007. Specifically, EN ISO 14971:2012 revision contains modifications that are intended to aid in the identification of remaining discrepancies between ISO 14971:2007 and the Essential Requirements for medical devices as contained in the pre-existing EU medical device directives. Further, EN ISO 13485:2012 specifies the risk management requirements and points to EN ISO 14971:2012. These two harmonised standards are complementary in nature therefore should be referenced. Section 5.2.3 introduces the topic of risk management. It would be beneficial for the EMA to combine the risk management topic and use of EN ISO14971 as a recognized standard in the same paragraph to ensure clarity of the guidance document.	
20	245	Use of harmonised standards to demonstrate compliance to Medical Device Directive 2007/42/EC is not mentioned in this section. Rationale: It would be beneficial to state that harmonised standards may be used to demonstrate compliance to Medical Device Directive 93/42/EEC for delivery devices.	Revise the paragraph as follows: *However, in addition to this, the relevant essential requirements in Annex I of the Medical Device Directive 93/42/EEC also apply with respect to safety and performance related features of the device (e.g. a syringe forming part of such a product) and <u>compliance to harmonised standards under Medical Device Directive 93/42/EEC for medical devices are recommended</u>.*
20	247-253	Section does not specify that the manufacturer should assess	Add the following paragraph in line 249.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		known and foreseeable hazards associated with the medical device in both normal (intended use) and fault conditions. Rationale: Consistency with EN ISO 14791:2012 risk management standard.	*Manufacturer should assess known and foreseeable hazards associated with the medical device in both normal (intended use) and fault conditions.*
20	251	The guidance states "it is also important to consider that medication errors may arise when…c) patients or HCPs misuse the product". Rationale: The guidance should state, "accidentally misuse" product since purposeful misuse would be out of scope.	Revise the following sentence as follows : *…or c) patients or HCPs accidentally misuse the product.*
20	261	Manufacturers should systematically assess risks throughout development taking into account all known information. Rationale: Risk management should be conducted throughout the lifecycle of the products and should take into consideration all relevant information to ensure acceptability of the residual risks.	Add the following paragraph in section 5.2.4. *Manufacturers should systematically assess risks throughout development taking into account all known information, which may include output from 1) post-market experience with similar products, 2) human factor engineering/usability engineering studies, and 3) clinical experience (e.g. clinical complaints).*
20	306-316	The errors described here are not preventable by action on the part of the MAH.	There is a need to highlight this problem to prescribers. National competent authorities communicate the nature and scale of this problem to prescribers in order to address errors that are beyond the influence of MAHs.
20	318 -335	As above	How will some of the errors in this section be communicated to prescribers? How will action be taken?
20	321-322	It would be helpful to reword the text for clarity.	'…experienced breathing difficulties when ~~we was~~ prescribed prednisolone 40mg once daily for 7 days but was instead given propranolol 40mg once daily in error). Such errors may arise due to similarities in packaging…'

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
20	328	Another good practice is to ask the patient for his/her name and cross-check the information with the prescription or hospital order before administering any product.	
20	336 -361	When changes occur following referral concerning the preparation and administration, the updated modalities should be clearly explained in the new SPC/PIL in order to avoid potential errors. To note: (Line 361) Important to explain in SPC/PIL the different modalities in terms of preparation & administration for injection route: IV, IM, when applicable.	
20	431	The guidance should recommend use of the harmonised standard ISO 13485:2012 associated with the investigation of medication errors for medicinal product delivered via a delivery device; however the guidance should not dictate that any medication errors detected in the post-marketing environment be investigated. Rationale: EN ISO 13485:2012 harmonised standard states that an organization shall establish a documented procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes. The requirement to perform a root cause investigation for **any** medication errors (as stated in the draft guidance) is not practical and may not be value-added. For example, a medication error associated with a medicinal product delivered via a delivery device might not result in serious adverse event therefore it would be reasonable for the manufacturer to monitor the medication error without performing a root cause investigation. A root cause investigation would be triggered when the same medication error	Revise the paragraph as follows : *A manufacturer should monitor ~~RCA should be conducted for any~~ medication errors detected in the post-marketing environment so that lessons can be learned from serious incidents which may in turn reduce the likelihood of future incidents.*

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		has reached a predefined monitoring threshold. We suggest to allow flexibility for the manufacturer to implement root cause investigation, corrective and preventive action in accordance with EN ISO 13485:2012.	
20	431-435	This sections seems to imply that root cause analyses, including what is proposed to be done, is to be summarized in the PSUR. Please delete – 'the PSUR is not intended for a discussion of root cause analyses, but to provide an assessment of the benefit / risk of a product, and discuss any changes in the benefit / risk during the period.	'A RCA should be conducted for any medication errors detected in the post-marketing environment so that lessons can be learned from serious incidents which may in turn reduce the likelihood of future incidents. ~~The PSUR and RMP can both be used to document and analyse reports of medication error related to the design, presentation, labelling or naming of the medicinal product and where the need for risk minimisation measure and or communication can be taken.~~'
20	444	When discussing risk control measures, mitigation/minimization strategies should be in line with EN ISO14971:2012 Rationale: EN ISO 14971:2012 describes the priority order to mitigate risks. Specifically, the priority of measures should be to initially try to design out problems, if not possible then include protective measures, if not possible then relying on warnings as last measure.	Add this paragraph in section 6.1: *For medicinal products with delivery system the following risk control options should be considered in the priority order listed:* *a) inherent safety by design;* *b) protective measures in the medical device itself or in the manufacturing process;* *c) information for safety.*
20	461	The draft guidance states that critical information should be included in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet. The draft guidance further states, "more prominent warnings should be included on the packaging…" The meaning of "more prominent warnings" needs clarification.	Revise the paragraph as follows : *It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or care givers or whether more prominent*

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		Rationale: "more prominent warnings" for a medicinal product can be accomplished by providing a "quick reference guide" that aligns with the SmPC and Patient Information Leaflet. The "quick reference guide" should be easy to read and contain relevant "prominent warnings" information.	*warnings should be included on the packaging <u>such as "quick reference guide"</u> so that these are not overlooked…*
20	471	Line 471 states that "the most common form of additional risk minimisation is educational materials for HCPs and patients…". As intended users may be more than HCPs and patients, we recommend to revise this paragraph accordingly.	Revise the paragraphs as follows : *The most common form of additional risk minimisation is educational materials <u>for intended users, e.g.</u> HCPs, <u>caregivers</u> and patients…*
20	481	Specify that the development of additional risk minimisation materials could also concern "mature" products when specific issues have been identified.	
20	482-483	Lines 481 – 483 state, "the development of additional risk minimisation materials should involve consultation with communication experts, patients and HCPs on the design and wording of educational material and that, where appropriate, it is piloted before implementation". As intended users may be more than HCPs and patients, Roche recommends the EMA to revise this paragraph accordingly. It is also unclear who "communication experts" are and the meaning of "piloted". Rationale: Intended Users may be more than patients and HCP and should be able to provide meaningful input into the risk minimisation materials. These materials, where appropriate, can be user-tested using a usability study.	Revise the paragraph as follows (see the underlined portions): *The development of additional risk minimisation materials should involve consultation with communication experts, <u>intended users (e.g.</u> HCPs, <u>caregivers</u> and patients<u>)</u> on the design and wording of educational material and that, where appropriate, it is <u>user-tested</u> ~~piloted~~ before implementation.*
20	485	This section describes sources of medication errors at the design stage, which is related to the contents of section: 5.2 (Assessing	Recommend moving section 6.1.1 (error prevention at product design stage) to section 5.2.1.1 (product design).

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		the potential for medication errors during the product life-cycle), where Human Factor (including user studies) and Risk Management are discussed. Rationale: It would be beneficial to consolidate guidance related to error prevention at product design stage in a single section to ensure consistency and clarity of the guidance.	
20	485	This section describes sources of medication errors at the design stage, which is related to the contents of section: 5.2 (Assessing the potential for medication errors during the product life-cycle), where Human Factor (including user studies) and Risk Management are discussed. Rationale: It would be beneficial to consolidate guidance related to error prevention at product design stage in a single section to ensure consistency and clarity of the guidance.	Move section 6.1.1 (error prevention at product design stage) to section 5.2.1.1 (product design).
20	489-490	"Applicants should proactively consider all aspects of the design of the product, how it will be used and 489 who will use it and conduct a suitable analysis of potential medication errors (see section 2.2.3)." Intended use environment is not mentioned in the guidance. **Rationale**: Human factor testing must consider all three elements – intended user(s), use environment(s), and use interface. Intended use environment is not mentioned in the guidance. Further, section 2.2.3 does not exist in the guidance. We believe that this is a typographical error.	Roche recommend revising the paragraph as follows (see the underlined and strikethrough portions): *Applicants should proactively consider all aspects of the design of the product, how it will be used, ~~and~~ who will use it, the intended use environment, and conduct a suitable analysis of potential medication errors (see section 5~~2~~.2.3).*
20	630	The sentence "as mentioned in section 2.2.3, human factor testing	Include the following paragraph in section 5.2.3.2 (L231):

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		can be very useful in demonstrating that instructions for use can be understood and followed without error." The statement is not mentioned in the human factors section 5.2.3.2. "Simulated use testing". Rationale: Section 2.2.3 does not exist in the draft guidance and it is likely a typographical error. The human factor section 5.2.3.2 (simulate use testing) does not state the guidance provided above.	*Human factor testing can be very useful in demonstrating that instructions for use can be understood and followed adequately.*
20	663-664	In addition of the "important role in determining that the treatment is appropriate for the patient", add also the importance of the role of the prescriber to explain to their patients, the route of administration and also to verify if this route is appropriate for their patients. Importance of the educational role of the MAH for the prescribers and pharmacists in particular when products have specific modalities of preparation and administration in order to avoid potential medications errors.	
20	717	" GP training"	Please write out abbreviation.
20	775	'DUS' should be defined.	Please write out abbreviation
20	792	Add a paragraph concerning the specific considerations/precautions to take for medical products with a narrow therapeutic range	
20	808-809	Reference 26 does not seem to substantiate this sentence "For liquid oral medications there is some evidence that oral syringes may be the most accurate dosing device"	Please check reference and correct
20	809-813	Appears to contradict previous sentence (808-809), which suggests that oral syringes are most accurate	Add "in adults" to previous sentence: *"For liquid oral medications there is some evidence 808 that oral syringes may be the most accurate dosing device <u>in adults</u>"*

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
20	829	Delete the word “both” as renal metabolism is only important for a small minority of drugs	“systems, ~~both~~ vital for metabolism and clearance”
20	851-853	Describes issues related with the administration of insulin but it would be recommendable to include some solutions. For example: “Older patients with diabetes may be more likely to have impaired eye sight than younger patients which may have implications for the correct use of insulin pens, **and in that case patients should be encouraged to get support from a caregiver**.	
20	1113	Not all errors described in the “implants” section of Annex I is attributed to design. Some of the errors modes described are use-related. For example, “insertion of the device or its removal” and “insertion in the wrong place” are use-related errors, not design related errors. Further, “Implants”, as referenced in line 1113, refers to medical devices (CE marked). Implants are not considered medicinal products. Rationale: Use-related errors should not be included in Annex I as it describes sources of medication error in medicinal product design. The scope of the guidance pertains to medicinal products, not medical devices that are CE-marked.	Delete the section “Implants” from the guidance to avoid confusion between design error vs. use error and medicinal product vs. medical device.
20	1124	Mentioned example of Timolol is not considered a medication error in the current definition. Also in general mentioning product specific examples do not have an added value in the context of this paper	• Delete particular example as this does not relate to a medication error but rather a manufacturing/quality issue. • Not to use product specific examples in general
20	1278-1280	Lines 1278 – 1280 states “clear instructions for use of inhalers	Revise the paragraph as follows:

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		(including diagrams) should be included in product information and along with reminder that patients should be shown how to use the device and that their inhaler technique should be checked regularly". Remove the redundant use "reminder" requirements. Rationale: The intent of the Instruction For Use (IFU) and other product labelling is to ensure that the patients can follow the use instructions adequately. The IFU and product labelling may be validated in a usability study. The reminder requirements seem redundant and defeat the purpose of the usability study.	*Clear ~~instructions for~~ use instructions of inhalers (including diagrams) should be included in product Instruction For Use (IFU). Additional training aids, other than the IFU, may be provided prior to the patients being allowed to use the inhalers. ~~information and along with reminder that patients should be shown how to use the device and that their inhaler technique should be checked regularly~~*
21	262-419	In most cases of the present draft the given example are helpful and explain the problematic of occurrence of medication as well as the measures needed to avoid them very strikingly. Furthermore, the risk minimization measure to reduce medication errors and to improve the safe use of the drugs seems to be appropriate, especially with regard to the relation of risk/potential harm of the drug. As exception the example starting at line 340: lack of efficacy was reported with leuprorelin suspension for injection due to errors in the preparation, mixing and administration of the product, requiring amendment of the instructions for use/reconstitution. Compared to the other examples in this subchapter this example gives no further information/insights in the issue regarding "Preparation and administration". Hence, this example should be omitted. **According to section *2. Scope***, this guidance outlines the key	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		principles of risk management planning in relation to medication errors arising from the medicinal product (such as those related to the design, presentation, labelling, naming, and packaging). However, there are several of aims described in this guidance, which are mainly addressed to the prescribers and the health care professionals rather than to MAHs. Design, presentation, labelling, naming, and packaging of a drug have only minor impact for avoiding medication errors here. Careful daily work, appropriate use, and good organization seems to be the most effective measures to avoid medication errors. Two examples are given below: **310-316** ISMP has previously 310 published a call to action to eliminate handwritten prescriptions and this focused on eliminating the use of error-prone abbreviations by healthcare professionals. **327-330** It is also possible that a prescription may be dispensed to the wrong patient altogether, particularly in the hospital environment or care home. Good practice to avoid such errors could include asking a patient specifically if the product they have been dispensed is the one they usually get and checking that it is the product generally recommended in treatment guidelines.	
21	1114-1117	Under Implants, insertion of the device in the wrong place is listed and dexamethasone eye implant misplacement is given as an example for this medication error. Therefore it is unnecessary to refer to dexamethasone in this case since misplacing an eye implant may happen irrespective of the active ingredient contained	Implants Some products are implanted into the body (e.g. contraceptive implants for insulin infusion pumps) and there may be errors associated with the insertion of the device or its removal, insertion in the wrong place (e.g.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		in it.	dexamethasone eye implant misplacement), devices moving or breaking internally (and perforating tissues), or becoming difficult to locate.
21	1122 – 1126	Under Topical products, reference is made to the design of single-use droppers for eye drops that impose a risk when they leave sharp edges after breaking off the tip for use. This is a general and well-known risk related to this particular pharmaceutical form. Therefore, while the example reported in July 2013 is a valid case, it is not justified to cite a specific medicinal product by mentioning the active ingredients and the date when this was reported.	Eye drops are often presented in a bottle or individual single-use droppers but these can be difficult to hold and use for patients with manual dexterity problems. Related to this, single-use droppers which are broken open to use may leave sharp edges, which could damage the cornea (e.g. as with timolol and dorzolamide eye drops after the introduction of a new design of dropper, reported in July 2013).
21	1127-1129	As the volume of the conjunctival sac is limited larger amounts than 15 – 20 µl rinse out of the eye and have to be removed e. g. by a tissue. Therefore a large drop size resp. a large amount of eye drop solution is rather a risk for the surrounding skin of the eye than related to the eye / eye disease.	For drops presented in larger bottles, instructions for use vary and patients may squeeze the bottle excessively and deliver a too large amount of solution an overdose which could have a noxious effect on the skin close to the eye serious consequences particularly if administered at a too-high dose for a prolonged period.
22	306-312	The list of potential issues with prescribing can possibly be improved with addition of other rules when prescribing.	See in Appendix 1 the NHS Lothian Golden Rules of Prescribing attached as an example of other elements core to good prescribing rules that might be considered.
22	337-360	Support the inclusion of specific examples to illustrate issues that have occurred in practice but very long.	Suggest that descriptions be shortened.
22	424	Root cause analysis is a methodology that is well known universally, however, the term applied to the whole process in Scotland is “adverse event review” (i.e. RCA is a tool applied during the investigation process). It is also positive to note that the consultation document refers to	Please review terminology applied to adverse event review process as a whole and refer to the range of potential methodologies

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		adverse events – this aligns with Healthcare Improvement Scotland's adverse event framework. The good practice guide could also include reference to other methodologies used in adverse event review such as fishbone diagrams, timelines, contributory analysis, as quite often there is no one root cause but a variety of factors together result in the adverse event. The HIS Adverse Events Framework is available from http://www.healthcareimprovementscotland.org/our_work/governance_and_assurance/management_of_adverse_events/national_framework.aspx	
22	462-465	The example of piperacillin/tazobactam is okay but we think another example with wider risks across primary and secondary care would be better.	Celgene (thalidomide) 50mg packaging warning.
22	495-498	Strongly support this inclusion.	Suggest use example of Relvar inhaler colour safety concern and subsequent change here.
22	530-533	This error risk not unique to Ireland. Any country within the EU using these trade names has the same issue.	Make applicable to EU countries with the same trade names. Another example of two medicines frequently confused is "hydroxyzine" and "hydralazine" with significant clinical risk when confused and taken by a patient.
22	592-593	This is very important since many errors occur when company product 'branding' have more than one strength of a medicine and the packages all look similar.	Colour coding of packs for different strengths of the same medicine from any one manufacturer should make differentiation between different strengths easier.
22	602-606	The increased font size should not just apply to "high risk" medicines. This should be a standard for all medicines with multiple strengths of a product available.	As above
22	654	Use of the term "medicine cabinet" is an issue of concern from 2 perspectives: 1) most patients do not have a dedicated "medicine	Please review and consider above concerns.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		cabinet" so is this recommendation practical; 2) If referring to a bathroom cabinet then this would not be the preferred environment for medicines due to the moisture content of bathrooms.	
22	656-657	Patient web-based pill identifier is a concern since even when the TicTac tablet identifier is used by healthcare professionals in the UK there is still a risk for users due to colour distortion; and with plain, white tablets accurate measurement is an issue so major risk for these tablets.	Please reconsider advocating such web-based information being promoted directly to patients since it will carry its own risk.
22	681-683	Pharmacists should also be counselling on possible common side effects to expect; and counselled on any signs of a serious side effect so they know when to seek advice quickly from their physician.	Request that is added since this is a professional obligation of pharmacists.
22	684-708	Items listed are relevant but 2 gaps that could be added: 1) Reconstitution or dilution with incompatible solution; or incorrect quantity of solution to make incorrect concentration for administration 2) When it is critical that the mg/kg dose is considered so maximum doses not exceeded (e.g. IV paracetamol) but body weight not recorded.	Please consider adding.
22	714-739	Does not cover transition of care error solutions and issues with medicines reconciliation between care interfaces.	Please consider.
22	810-813	This example is a little confusing. Do you mean here when a syringe with the incorrect graduations available to measure the dose? The example as it stands suggests that a 1mL syringe with 0.1mL graduations is not as safe as a 1mL dropper which is not accurate.	Please review and amend as required to make clearer.
22	870-874	The most obvious example of medicines used in this patient population would be eye drops. At present he font size on eye drop	Please consider using the example.

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		containers are a major issue since containers so small that bigger font size may be difficult.	
22	911-912	The preferred option is cascade via 1 route only so less likely to be missed; and less multiple receipt of information.	Please consider preference for recommendation.
22	984-992	Need to make clear that it is not expected that patients and healthcare professionals would report via industry and the national pharmacovigilance reporting scheme (e.g. In the UK a report via the Yellow Card Scheme preferentially; and if reported via this route duplicate reporting via industry not required. The unique Yellow Card reference number could be given to industry instead if requested for their cross reference).	As described.
22	1054-1055	Maximum tablet size should be set for manufacturers that is suitable for oral administration since there have been cases of patient unacceptability for swallowing due to size of tablets that has resulted in non-compliance with medicines in high risk disease states (e.g. HIV).	
22	118	Extra "."	Please delete
22	1152-1165	Missing from this section is the issue when different displacement values are present with generic equivalent medicines that can result in errors in practice.	
22	1201	Currently blank but another example of relevance that you might wish to add here is that of citalopram drops (i.e. it is not always explicit on external packaging for all generic brands the equivalence of drops to mg is for the product.	Please consider addition of the example.
23	70	ANSM considers the term "failure" present in the definition of medication error is not relevant, because related to a fault of the health-care professional,	
23	72	ANSM doesn't agree with the use of the term "harm" in the	"Harm" should be deleted and replace by "consequences for

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		definition of medication error, and proposes to replace it by the broader term "consequences for the patient".	patient"
23	71	ANSM considers that the proposed definition of medication error is very restrictive in the scope. Indeed, several steps should also appear in this guideline, such as storage, preparation, therapeutic and clinical follow-up and transmission of medical and pharmaceutical information.	
23	428	This guideline seems to be intended for MAH, it should be more pragmatic, and some concepts should be deleted, as multidisciplinary analysis of the causes of errors at a local level concerns the healthcare professionals. Consequently, ANSM considers to remove in this guideline this mention in order to avoid ambiguity about the role of the MAH. A dedicated paragraph, intended for HCP could also be added in order to highlight the need for RCA.	
23	672-683	As mentioned above, pharmaceutical analysis of prescriptions and the advisory role of pharmacists are presented as risk minimization tools. However, presentation is confusing since the guideline seems to be intended for MAH.	
23	711	ANSM is of the opinion that the use of a delivery device is a cause of error not a type of error.	
23	232-236	ANSM proposes that the simulation tests of use "Simulated use testing" proposed should be accompanied by a standardized method.	
23	794-841	Regarding the paediatric patients: the main sources of medication errors are not mentioned, especially the possibility of confusion between adult and paediatric forms, and the lack of harmonization between available forms and delivery devices.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
23	843-868	Regarding the elderly patients: the main sources of medication errors are not mentioned, especially problems related to the handling of products (taking the tablets, divisibility of tablets, counting drinkable drops) and dose adjustment based on renal and hepatic function for example.	
23	1083; 1091-1093; 1100-1104; 1241-1242;	All the examples not concerned by medication errors must be deleted from this guideline, such as: domestic accident involving a child accidentally swallowing medicine (if any):	
24	84	Spelling mistake	In ~~in~~ most cases medication errors are preventable…
24	158-160	Sentence should be rephrased; namely potential medication error that does not lead to harm or is already recognized and sufficiently minimised by appropriate routine activities should not be captured in the RMP as important risk.	
24	159-160	Spelling mistake	…may be in place ~~in place~~ to reduce…
24	182-187	By definition generic drug has same indication and similarity in posology, method of administration, strength or packaging. Therefore, it should be clearly stated that potential of medication errors does not refer to generic. Moreover, medication errors in the context of the therapeutic armamentarium are possible, but usually not due to similarity; they are mainly possible due to differences in posology, appearance, method of administration or strength for products having the same indication. On the other hand, medication errors are possible due to similarity in name and packaging for product with different indication.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
24	182-187	More clarity would be needed with the following: Medication errors in the context of the therapeutic armamentarium are possible, but usually not due to similarity; they are mainly possible due to differences in posology, appearance, method of administration or strength for products having the same indication. On the other hand, for products with different indication medication errors are possible in case of similarity in name and packaging. Furthermore, by definition generic drug has the same indication and similarity in posology, method of administration, strength or packaging. Therefore, it should be clearly stated that potential of medication errors does not refer to generic medicines.	Complete paragraph should be rephrased to reflect the above comment.
24	267 - 316	Please consider to add some information on the following: Medication errors are also related to multiple prescriptions of medicinal products of the same class by different specialists. There exists a clear need of a current prescription overview on patient level, including OTC dispensing. As well, this should be addressed to national health systems.	
24	321	Spelling mistake	…experienced breathing difficulties when ~~we~~ he was prescribed prednisolone 40mg once daily for 7 days but…
24	383-388	Please consider to add the following source of omission: Source of errors of omission may also result from a legal restriction where a pharmacist might not be able to supply a patient with the long term (Rx) medication while the patient forgot to get a new prescription, especially during holiday times when the general practitioner is not available.	
24	486-492; 609-611	Please acknowledge the following: In order for companies to be able to address the potential for mix-	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		ups by comparing the product design (appearance) of the medicines already on the market, approved Mock-ups of the registered/marketed medicines should made publicly available. Based on such publication MAHs would be able to develop a design that could appropriately address concerns described in this guide.	
24	510-512	It is not clear to which cases alternating use refers to. We would appreciate to have an example or to make this sentence clearer, having in mind that companies have a legal possibility to either choose Brand name or INN name for their medicinal product.	
24	538-544	It should be acknowledged that in case of nationally authorised (MRP/DCP) there is no system established as it is for centrally authorised products (CAP) (i.e. Name Review Group) to review the proposed invented name. It is therefore extremely challenging to find an acceptable brand name for generic medicines and is as well time and resources consuming. It would be therefore of an added value to have one system, which would apply for all medicines, regardless of their legal basis. This could mitigate to some extend medication errors arising from the name of the medicinal product. It would be therefore welcomed if some guidance for MRP/DCP authorised products would be given, not only for CAPs.	
24	695	It is not clear what it is meant by “Dispensing a medicinal product of **inferior quality** (pharmaceutical companies)”. Question arises how exactly marketing authorization of a product of inferior quality could be approved by a competent authority and is then actually made available at pharmacies to be dispensed. Although it is clear the guide is summarising a survey outcome that was performed in hospital pharmacies, a term as such could lead to wrong conclusions.	Delete this example or rephrase it so it will reflect the comment.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
24	724	Comment: spelling mistake	Guidance ~~in~~ is intended only to…
24	1205-1207	Differentiation by size is not mentioned in the EMA's Q&A but is included in this Good practice guide. From that, one could conclude that additional differentiating parameter (size) is requested, which could be misleading.	These lines should be re-written in line with the EMA Q&A on tablet appearance which states: *In the case of applications for more than one tablet strength, the different tablet strengths should be distinguishable at a level sufficient to avoid mistakes between the different strengths by the final user. Distinguishing tablet strengths by colour/ shape and marking/ embossing is preferable.*
24	1315-1317	We strongly disagree with the proposed consideration focusing only on biosimilars. There should be no differentiation in packaging requirement between originator and biosimilar medicinal product i.e. the same requirements should apply to all biological medicines. There is no scientific nor legal reason to request distinguishing packaging for biosimilars only. Furthermore, all approved biosimilar products in the EU have been evaluated centrally by the EMA and approved by the European Commission and had to comply with Art 54-57 and 61-63 of Directive 2001/83/EC. Indeed all biosimilar packaging components are assessed by the EMA and need EMA approval prior to production. We therefore believe that singling out biosimilars is discriminatory. Article 102(e) of Directive 2001/83/EC provides legal framework for Member States to ensure that all biological medicines are clearly identifiable for the purpose of pharmacovigilance which covers also appropriate prescribing practices. Any prescribing recommendations or guidelines are indeed within the competence of member states and therefore are out of scope of this EMA good practice guide on	Remove the proposed general consideration.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		risk minimisation and prevention of medication errors. This guide may eventually refer to the Commission Implementing Regulation of the cross-border health care directive which stipulates that for cross-border prescriptions biological products should be prescribed by their brand name.	
26	71	The statement can be made more specific and explicitly spell out the involvement or not of a medical device	Dispensing or administration of a medicinal product **(using or not a medical device)**
26	72	Reference to a caregiver (which are neither HCP, patient or consumer) is lacking	Professional (HCP), **caregiver,** patient or consumer
26	77	Link to role of competent authorities pertaining to the device is not outlined	~~and~~ Regulation (EC) 726/2004, chapter 3, Article 28**, and Directive 93/42/EEC, Article 10.**
26	93, 150	It is unclear what is meant by packaging, in particular whether "functional" packaging, i.e. device component of a single integral product, is in scope.	naming, **device component (if applicable)** and packaging
26	143	Not only different administration device, but also method of supply of administration device (i.e. if change from administration device co-packed with the medicinal product to "recommended" administration device, thereby increasing the chance of selecting an inadequate administration device).	**Method of supply of administration device**
26	154	What is understood by device failure is unclear. Does the document only consider single integral device/medicinal products considered? Also refer back to general comment provided in section 1 of this document.	The effects of device failure **(device component forming an integral part with the medicinal product as well as co-packed medical devices)**
26	199-200	What is meant by "presented" with a device is unclear. Is it co-packaged and/or recommended for use with the medicinal product?	Depends on response to question
26	201	Which 'instructions for use' does this refer to: of the MP and co-packed device, of the MP forming a single integral product with the device? Refer back to general comment provided in section 1 of this	Depends on response to above question

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		document.	
26	218	The standard IEC 62366 is not only applicable pre-authorisation but throughout product lifecycle. It should not be confused even though only cited under section 5.2.3 "…Pre-authorisation"	should also be followed **throughout the administration device lifecycle (from development to decommissioning)**
26	235	Rather than simply providing human factor testing reports, is it encouraged to consult EMA when the human factors testing protocol is developed?	Depends on response to above question
26	238	Comment: It would valuable to also consider co-packed medical devices, i.e. cover all scenarios directly in the guideline to. Refer back to general comment provided in section 1 of this document.	Depends on response to above question
26	387-388	Some of the errors cited, and in particular the example about transfer between different units cannot be influenced by the MP manufacturer, and it is not clear how relevant this can be in this guide. Please re-confirm the targeted audience of this guideline, and otherwise remove example when the MP manufacturer cannot have any influence during development & maintenance of a MP on the market.	
26	469	What referring to the "burden" of additional risk minimisation measures? This has a negative connotation where in fact the risk minimisation measures are intended to reduce medication errors. Would it be possible to rather refer to the need to assess the effectiveness of the foreseen risk minimisation measures to demonstrate their added value?	Additional risk minimisation measures should focus on the prevention of medication errors**. Where possible their effectiveness shall be evaluated prior to implementation.** ~~but the burden of imposing such measures on patients, HCPs and the healthcare system should be balanced against the benefits~~.
26	490	The environment in which the product will be used may also have an impact (for example clinical environment versus home environment…).	How it will be used**, in which environment it will be used** and who will use
26	744	Near misses shall be reported if related to a co-packed medical	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		device. Directive 93/42/EEC, as amended applies. Is it foreseen to implement mechanism to link the pharmacovigilance and vigilance databases and make the link between related drug and device reports?	
26	1114	Do “contraceptive implants for insulin infusion pumps” really exist? Or did you mean “contraceptive implants or insulin infusion pumps”	Contraceptive implants or insulin infusion pumps
28	209-211	**Areas where the guidance should go further** *B) Tools for improving product design* In lines 209-211 of the guidance document, reference is made to a variety of tools for improving product design including: • ‘failure mode and effects analysis’ (FMEA); • ‘simulated use testing’; and, • ‘perception- cognition-action’ (PCA) analysis However the guidance document does not provide the reader with a clear sense of the EMA’s position on these tools. Is the guidance recommending all or any of these tools be used? A clearer statement of the EMA’s position and recommendations on this aspect of product design could improve the value of the guidance document.	
28	317-335	**Areas where the guidance should go further** *C) Preventing dispensing errors* Lines 317-335 of the guidance document describe the errors that can occur at dispensing stage, including incorrect selection of a product, and labelling mistakes.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		This is another area of the document where EAHP identifies opportunity to increase value by strengthening the clarity of recommendations e.g. on organisation of the dispensary, lighting, physical separation between different formulations, double check of all dispensed medicine, use of barcoding etc).	
28	346	**Areas where the guidance should go further** *D) Potassium Chloride* In line 346 of the guidance document mention is made of existing national recommendations on the stocking, handling and labelling of concentrations of potassium chloride. However no specific reference or links are made to these. This could be a valuable improvement to the final guidance document for the reader who desires to be better informed about the mentioned recommendations.	
28	1036	**Suggested areas for improving the presentation of the guidance** Annex 1 of the guidance document, detailing how the specific design of the medicinal product (e.g. tablet, oral solution, patches) can be separately associated with specific risks, is a well-compiled reference. Accordingly, it strikes EAHP as constituting the basis of helpful educational material for healthcare professionals, patients and industry stakeholders, if supported by some visual illustration and/or summarising tables.	
28	158	When a potential risk of medication error has been identified, medication error should be captured in RMP (risk Management Plan):	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		We should be able to see this for NHS products	
28	232-233	There is currently no legal requirement for user-testing of instructions for use or administration or; reconstitution of medicines in order to investigate the potential for medication errors. This should be a requirement of Product Authorisation?	
28	431-434	A RCA should be conducted for any medication errors detected in the post-marketing environment so that lessons can be learned from serious incidents which may in turn reduce the likelihood of future incidents 'Not 'any' but selected, based on the capacity for learning and minimisation of future error, risk assessment framework NPSA	
28	459-463	It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or care givers or whether more prominent warnings should be included on the packaging so that these are not overlooked, e.g. desmopressin. This needs to be informed by Patient Safety Incidents received by National Reporting and Learning Systems, implying much closer links between local practice with Industry in the future.	
28	495	Look alike and sound alike names of medicinal products which could pose a risk to patients' safety, should be avoided. There is a function/naming relationship that need to be taken into	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		account in this. The evidence for the name to imply function as a mechanism for patient safety is weak	
28	640-1	Key to risk minimisation and prevention of medication errors is the provision of a suitable PL which describes the correct use of the medicinal product. Assumes that healthcare professionals actually read PLs, which in my experience they do not. There needs to be more than this. There need to be a level of system barriers to doing the wrong thing!	
28	592	Colour differentiation, which makes certain features stand out, or helps to distinguish one item from another Useful as a consideration for distinguishing short, medium and long-acting insulins	
28	721-722	In recent years there has already been increased use of technology in prescribing and dispensing systems. Such new technologies go beyond the regulatory tools for mitigating the risk of medication error (which are the responsibility of national competent authorities and MAHs) Is the MHRA responsible, if not who is?	
28	431-243	A RCA should be conducted for any medication errors detected in the post-marketing environment so that lessons can be learned from serious incidents which may in turn reduce the likelihood of future incidents.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		Impractical , there are far too many errors for this to be undertaken, rather it should be the requirement for serious harm	
28	461	…more prominent warnings should be included on the packaging so that these [latent errors] are not overlooked Fully support this as a way forward, but it needs to be managed and used sparingly for known error-prone situations	
28	665-6	The use of pop-up reminders in e-prescribing systems may be useful in reminding the prescriber to specify details of the prescription e.g. strength of insulin. We agree on the utility of reminders but evidence demonstrates that the effectiveness depends on perceived relevance and frequency. The best way is to force acknowledgement of the safety of the prescribed item, but this need to be reserved for known safety issues, such as daily MTX, penicillamine not penicillin	
29	138-146	Add: “product name” (Explanation: The product name is important with regards to both identification of a product but also differentiation of products with different features when needed).	
29	602; 628	Ref above general comment: It may be equally necessary to distinguish different formulations (immediate/modified). Is it possible to agree on a common, recognisable element that may be used both for CAPs and NAPs?	
30	254	Typo	Delivered via a device.
30	538-540	Unclear / repetition of scope? Is the NRG only considering CAPs and comparing these with CAPs?	If that is true then it is correctly written, however seems unlikely.
30	1118	Typo	Remove bullet.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
30	1238	Typo	Not rather than now
30	1310	Unclear guidance, if I read this correctly the SmPC for a product should refer and clarify differences between this SmPC and that for the other indication (strength in hybrid products)	Clarify.
31	14-16	Answer = Yes	
31	671	No mention in the role of the pharmacist in carrying out an assessment of the clinical suitability of the medicine.	We would like to see the use of the word "clinical" in the description and pharmacists mentioned in assessing the clinical, legal and safety suitability of the medicines.
31	675	Statement "it is important to be discreet and not to undermine the confidence of the patients in the prescriber"	We agree with this of course but this needs to be qualified. The role of the pharmacist goes beyond simply cover for an error in prescribing.
31	684	Errors in hospital pharmacy are identified (research piece referenced).	Is there anything to demonstrate the main errors in community pharmacy? We realise that they will be similar but the consultation is quite focussed on the hospital setting.
33	5	“Errors” is suggestive of blame and a punitive culture rather than fair blame and a learning culture. I suggest using incidents throughout rather than errors.	“Incidents”
33	71	People also make mistakes by giving the wrong or incomplete advice about medication so I think advice should also be included at this point.	
33	86	I am not convinced about that this when most incidents occur I think a new product is more likely to be reported than an older more established product.	
33	138	This list needs to include the name as there are too many look a like sound a like medications. Also pack sizes should be in multiples of 28 or course if used as a course– this is to reduce the numbers of medication strips which	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		are cut up leading to risks in decanting medication.	
33	193	I am also aware of errors where during a clinical trial the appropriate monitoring was not done leading to significant patient harm ie the renal function deteriorated was not checked and the drug continued to be administered leading to the death of the patient.	
33	316	Errors also arise from prescribing once daily doses for example a once daily IV antibiotic prescribed at 9:05 will not appear on the administration system until 9:00 the next day leading to problems of sepsis.	
33	330	Checking the product is generally recommended in treatment guidelines is not realistic at the point of dispensing.	
33	356	Exact same thing happens with older formulations such as Zuclopenthixol acetate and decanoate.	
33	388	Good place to mention prescribing once only doses often prescribed but prescriber does not tell nursing staff and so they are not administered or at least delayed administration of critical drugs.	
33	483	Qualitative approaches to analysing the pilots will yield richer data.	
33	489	Pre-printed tables of calculations of weight and dose or rate etc. could be included to help minimise calculation errors.	
33	506	Use of stems is valuable but there are some contradictions such as salbutamol and propranolol I have seen these confused.	
33	517	Very much support Tall Man lettering	
33	657	Need to mention patient‘s role in minimising problems when people are transferred between care settings e.g. “message in a bottle” or accurate lists of current medications and allergies.	
33	696	Also wrong or missing patient information leaflet.	
33	708	Wrong incomplete verbal information or not giving information at	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		all.	
33	773	It is the patient's that need the education- what about a CD showing them how to administer the patch.	
33	786	Again I think a qualitative approach would be more revealing about the sources of problems than a survey.	
33	796	As mentioned before charts with pre-calculated dose from strength and body weight in the SPC would reduce calculation errors.	
33	934-969	This lacks any emphasis on creating a learning culture- think it needs to be made explicit.	
33	1011-1019	The is a mixed methods (qualitative and quantitative) approach to evaluation and needs some social science input to give it the appropriate rigor and to really understand how human factors are involved.	
33	1049	What about not stopping medications abruptly e.g. Clozapine , steroids, sodium valproate etc. this can be done by both HCP and patients.	
33	1069	Presence of a desiccant which has sometimes been taken inadvertently. Also tablets being placed into monitored dosage systems too far in advance leading to deterioration.	
33	1078	Need to include confusion between different strengths of solutions e.g. Morphine is available in both 10mg/5ml and 100mg/5ml Could also mention accidental parenteral use of oral solutions e.g. sodium valproate use of oral purple barrelled syringes.	
33	1127	Confusion between eye drops and other solutions e.g. Olbas oil administered inadvertently to the eye.	
34	Whole document, *e.g.* lines	A large number of examples is used to illustrate different types of medication errors. The examples are useful, but result in a voluminous document.	It may be considered to include the examples of medication errors in a separate Annex. References to scientific reviews may be added to the Good Practice Guide and/or the

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
	280-305, 340-360, 684-712		Annexes to provide further background.
34	116-419	For the sake of readability of the Good Practice Guide it is advisable to separate the general principles of risk management planning and the tools used (5.1, 5.2.3, 5.2.5.1 and 5.2.5.2) from the potential sources of medication error (5.2.1, 5.2.2, 5.2.4 and 5.2.5)	Restructuring of section 5.
34	443	The title of chapter 6 “Measurement of success of measures taken” does not cover the content of the chapter.	Adapt the heading into a more general heading, for instance “Risk minimisation measures”.
34	Whole document, *e.g.* 280-305, 340-360, 684-712	A large number of examples are used to illustrate different types of medication errors. The examples are useful, but result in a voluminous document.	It may be considered to include the examples of medication errors in a separate Annex. References to scientific reviews may be added to the Good Practice Guide and/or the Annexes to provide further background.
35	116-419	For the sake of readability of the Good Practice Guide it is advisable to separate the general principles of risk management planning and the tools used (5.1, 5.2.3, 5.2.5.1 and 5.2.5.2) from the potential sources of medication error (5.2.1, 5.2.2, 5.2.4 and 5.2.5)	Restructuring of section 5.
35	161	This also applies to DSURs, where overdose, patient compliance, misuse and abuse should be discussed.	Add reference to DSURs
35	196	There are further useful examples of common errors we have seen in clinical trials	Add example: common medication errors can also occur in clinical trials where multiple dose strengths are placed in the same secondary packaging, with very similar primary packaging. This can lead to overdose or underdose if the incorrect strength is taken by the patient.
35	203	Additional information would be useful here to demonstrate how this can be monitored during the trial.	Add – Pharmacovigilance can play a vital role in monitoring medication errors during the trial. For example if

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			medication errors are captured and analysed through the trial, risk can be further minimised. For example in one trial the PV group noted during trend analysis that there were an increasing number of overdose events. Root cause analysis determined that this was related to poor packing design, where patients were provided with multiple dose strengths in one secondary package (carton). A number of patients that were on the low dose of the drug were unnecessarily receiving large quantities of the higher doses, simply to make the drug supply easier. This resulted in confusion and overdose – the packaging was therefore amended.
35	1211	The colour coding in the UK is a useful example, however for clinical trials this has caused problems. In a multinational trial patients who were familiar with warfarin took part in a clinical trial where warfarin was provided, but presented in different colours and strengths to the usual clinical supply, this contributed to overdose problems in the trial	The colour coding is a useful example, so should be kept in, however a word of caution for use in clinical trials should be added.
36	297	We suggest to add: in accordance with the law of each Country since in some Countries only medical doctors are authorized to draw the recipe (e.g. In Italy the prescription is made only by medical doctors)	
36	359	We suggest to add : It could be very useful to develop a system to collect data regarding the medicinal used by the patient at hospital level, at health care facilities and home care through community pharmacies; developing a network among general practitioners, pharmacists and hospital specialists in order to have more information on the treatments received by the patient.	

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36	362	We suggest to recall the importance of a dedicated area in the hospital pharmacies for anticancer drugs preparation under the pharmacists responsibility.	
37	146	It is important to add the iv drug stability after the reconstitution or the dilution and the stability of the vials after opened. It is necessary to have information on the possible concentration to use (mg/ml). Without this information, there is the risk to prepare concentrations of drugs not stable or not safe for the patient. In Italy all the preparation made in the pharmacy are compounded according the good preparation practice. When the preparation is made in the wards by nurses it is important to define the same level of good practice. For the oncological drugs the preparations need to be centralized in pharmacy units only. The same for paediatric drugs preparations or high risk medications. The process of drug preparation and administration needs to be standardized with procedures that can guarantee good practices and the correct stability of the drugs, both when the preparation is centralized in the pharmacy or when is made in the words.	
37	179	Sometimes some important information is present in the secondary packaging and not in the primary packaging with high risk of medication errors. For example, Nimbex 2 vials do not have the concentration in the vials, so it is possible to confuse (2 mg in total or 2mg/ml).	
37	314	We suggest to add that the software for the drug prescription needs to be evaluated by a health care team include physicians, pharmacists and nurses. It is important to validate/certificate the	

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		software to avoid the potential risk of errors and to test the software before the utilization.	
37	494	Paragraph 6.1.2: We suggest having a national formulary with the drug pictures (both primary and secondary package) to help health care employee in preventing LASA. We suggest adopting a unique 2 D barcode in which it is included lot and expiration to guarantee a better traceability of the drugs. Implement the checklist use, to make a double check on specific processes at high risk of errors and a double control in high-risk medication prescription, preparation and administration processes.	
38	84	Spelling mistake: (In in most cases)	
38	196-197	Examples such as the use of small font sizes and absence of information on dose/strength are given as common sources leading to medication errors in trials. Have multi-language labels not given any medication errors? The use of multi-language often leads to the use of very small font size and precautions and warning hide in a small multi page label.	Include the use of multi-language labels as an example of the source for medication errors.
38	267	Using generic drug replacement when collecting the prescribed medication at the pharmacy often leads to confusion among patients (often elderly patients). When patients are given a new prescription, they sometimes collect the prescribed medication before all of the “old” medication is completely used up. Although the patient are given the same drug (active ingredient), the name of the product and colors of the package handed over by the pharmacy can be different. Patients then could believe they have a new drug they are supposed to take together with the “old” drug. Consequently, they are taking twice the dose they are supposed to	Include generic replacement as one of the sources for overdosing and dosing errors.

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		take until the “old” drug is gone.	
38	321	Spelling mistake: when we was prescribed prednisolone	
38	444	Se the comment to line 267.	Include a subparagraph on “risk minimisation when replacing generic drugs”
39	65-68	Delete the second paragraph as it does not contain information pertinent to the paper.	
39	82	This is a wide range - better to say with an estimated global annual cost exceeding €4 billion.	
39	83-84	Individual studies have reported inpatient medication error rates of 1.2% to 5.3% for inpatients admissions.	
39	125-126		: ~~It is vital that~~ ~~r~~**R**isk management planning in relation to medication errors **should be** ~~is~~ proactive and begin~~s~~ at a**n** ~~very~~ early stage in product development.
39	126	Medication errors can arise at any stage of **the** treatment process...	
39	138-146	The product name is important with regards to both identification of a product but also differentiation of products with different features when needed)	Add product name.
39	164	Not sure "covariates defining the treated population" will be understood.	
39	165	Not sure "ameliorating" will be understood given the EU audience.	
39	182	Is this over-complicating language? This should be avoided in a doc that is supposed to be a guide to stopping errors.	Medication errors in the prescribing, dispensing and administration of medicines.
39	279	Consider adding the information below. • Prescribing generically should only take place where appropriate. Some preparations must be prescribed by brand. Examples include: Ciclosporin. • The patient's intolerances and allergies must be established and	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		taken into consideration when prescribing. • Measures should be taken during prescribing to reduce the risks associated with polypharmacy. • Appropriate dose adjustments should take place to reduce the risk of adverse drug reactions. • Evidence-based loading protocols should be used where appropriate, for example, when initiating warfarin. • The dosage should be calculated correctly. • The time of administration, where clinically important, should be correctly stated on the prescription. • The quantity stated on the prescription, and the duration of therapy should be clinically appropriate. • Cautions and contraindications, based on an accurate medical history, should be considered during prescribing. • Drug interactions should be checked during prescribing and the risks managed appropriately. • Prescriptions for controlled drugs should include the appropriate information.	
39	Relates to both: 292-305 And 312-316 And 318-326 And Section 6.1.2.1”Na	The Norwegian Medicines Agency has over time received several reports on mix up between immediate release formulations and modified release formulations/depot. It is especially the name setting of “INN+ MAH” that in an electronic prescription setting puts the prescriber in danger of picking the wrong line – especially the name setting INN+ MAH for tablets that comes in both immediate release and modified release formulations. Recent examples is the oxycodone tablets (immediate and depot), where a mix up of these formulation may have serious consequences.	

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	ming" and section 6.1.2.2 "Labelling and livery" And 710 And 1042	We would like to challenge if there may be developed a standard suffix or name-setting for the modified release formulations to more easily distinguish the formulations – also by name. At patient level and HPC handling the mix up may potentially also be reduced by a standard design feature to be present on the labelling for the modified release products.	
39	306-316		Consider adding 'Handwritten prescriptions are also more likely to include incomplete information, as electronic prescribing systems can prompt the prescriber to include key pieces of information.'
39	307	Not sure we should use the QD example here - I have always understood QD to mean 4 times a day (as had all the pharmacists I asked; 1 did indicate they Googled this and found a reference to QD being once daily but had never seen it in UK practice. It could cause more problems than it solves retaining this reference.	
39	312-316		Consider adding 'some electronic prescribing systems do not detect errors.'
39	318-326	Consider adding the information:	The expiry date should be checked prior to dispensing. Original pack dispensing is preferred where appropriate. Some formulations are not appropriate to be included in compliance aids such as dosette boxes due to instability. Appropriate counselling should take place; Where appropriate, the delivery device supplied with the product should be used (for administration of oral liquids from multidose containers).

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
39	328-330		…usually get, ~~and~~ checking that it is the product generally recommended in treatment guidelines **or asking their carer or person responsible for taking care of the patient's medication as appropriate.**
39	331-335	New medicines started in hospital should be: • Communicated to the patient, carers, GP, community pharmacy, keyworkers, outpatient monitoring clinic, care home as appropriate to maintain appropriate supply and monitoring; • Appropriate counselling should take place on the new and existing medicines; • Reconciliation should take place with existing medication prior to admission; • Be checked for interactions and contraindications along with all other therapy; • Be of the correct dosage, pharmaceutical form, route of administration, frequency of administration; • Medication stopped during the admission should be clearly communicated to the patient, carers, GP, community pharmacy, outpatient monitoring clinic, care home as appropriate to include reasons for stopping; • Appropriate outpatient follow-up relating to medicines should be arranged on discharge; • The appropriate quantity should be supplied.	
39	343-347	Consider adding the information:	The correct diluent, route and infusion rate calculation should be used. There may be different prescribing protocols between different healthcare settings (for example, different hospitals use different infusion

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			prescription charts and prescribers may frequently rotate between hospitals). Concurrent administration should only take place with compatible products.
39	370		…route rather than by infusion **and should be given by the correct route.**
39	495-498		Look alike and sound alike names of medicinal products which could pose a risk to patients' safety should be avoided. The name of a medicinal product could be an invented name **(**not liable to **cause** confusion with **another invented name or** a common name (e.g. INN)**)** ~~or a common name~~ **or a common/scientific name** accompanied by trade mark or name of the MAH.
39	503		…pharmaceutical substances **(**active pharmaceutical ingredients**)**, including…
39	507		**The non-proprietary name (INN) should utilise** ~~Use of~~ common ~~'~~stems~~'~~ for products which are in related pharmaceutical classes (e.g. -azepam for diazepam derivatives, -bactam for beta-lactamase inhibitors~~, gli- for sulfonamide hypoglycaemics~~). **A list of all stems can be found on the WHO web site.**
39	512	Add the information:	Practitioner should prescribe by INN where possible as alternating between prescribing by brand and INN may lead to overdosing should the patient be treated by multiple products containing the same active pharmaceutical ingredient.
39	513-520	The flucloxacillin example is not a good one as anyone mixing up a	Delete 'however'.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		-cillin in this way should be struck off. Prochlorperazine and promethazine is a good example and should not have been named in such ways. Tall man lettering is a bad fix for names that should not have been accepted. Tall man lettering does not work in a lot of prescribing software especially in EU so we should avoid talking about it.	
39	522	The CHMP guidance is for brand and generic naming of medicines so we may want to move this reference to the start of the naming section.	
39	522-527	This information is repeated within the sub-section on brand-name. It is proposed to simplify.	The CHMP has issued guidance on the acceptability of names for human medicinal products processed through the centralised procedure15. **The review of names is part of the evaluation of the safety of medicinal products in the centralised procedure. In particular, it is considered whether proposed names may create a public-health concern or potential safety risks**. ~~This includes that the name should not convey a promotional message, have 'bad' connotations in any of the official languages, be misleading in therapeutic, pharmaceutical or composition terms or cause confusion in print with any other branded product or established INN~~. The MAH should take this guidance into account when proposing invented names to the competent authorities.
39	533	Might be a little better to get all the examples into a new Annex as it breaks up the message quite a bit (throughout the doc)	
39	538-544	Re-wording is suggested to avoid repetition of footnotes linking to same guideline. Also, it is recommended to make clear that the	For centrally authorised medicines, the potential for **name related** medication errors ~~arising from the name of the~~

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		aspects addressed by the NRG are those of the NRG guideline and not limited to the few examples currently included in the text.	~~medicinal product~~ **that may occur at any level of the medication use process (i.e. prescription, dispensing, preparation and administration)** is assessed ~~(for centrally authorised medicinal products)~~ by the EMA's Name Review Group **(NRG) on the basis of the guideline on the acceptability of names for medicinal products processed through the centralised procedure15**~~, who have issued guidance on this matter~~. ~~-~~ ~~The Group review the proposed (invented) name of medicinal products and considers whether invented names may convey misleading therapeutic or pharmaceutical connotations, be misleading with respect to product composition of the product, be promotional, cause confusion in identifying medicinal products, or create difficulties in pronunciation (or have any inappropriate connotations) in the different EU official languages.~~ **Amongst others this comprehensive review is aiming to ensure that proposed names:** **- do not lead to confusion in print, speech and handwriting with the names of other medicinal products or cause confusion in identifying medicinal products;** **- do not convey misleading therapeutic/pharmaceutical connotations or are misleading with regards to the composition;**

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			- are not promotional; **- do not create difficulties in pronunciation or have inappropriate connotations in the different EU official languages.**
39	545	To use packaging rather than livery to be in line with the main heading (6.1.2) and the legislation.	Change: 6.1.2.2 Labelling and ~~livery~~ packaging
39	586-597	This paragraph may focus more on the recommendation of the use of colour differentiation, bearing in mind that overdoing it may also result in packaging similarities, and especially since the colour-coding is usually limited to specific cases and/or not recommended by the experts. There is some example guidance stating that the use colour-coding is not usually recommended or should be limited (e.g. Expert Group on Safe Medication Practices[23], NHS guidance[24], draft guidance FDA for containers and carton labelling design[25]).	
39	602 and 628	(Ref above comment regarding immediate/modified release formulations (lines 292-305)). It may be equally necessary to distinguish different formulations (immediate/modified). Is it possible to agree on a common, recognisable element that may be	

[23] Expert Group on Safe Medication Practices http://www.coe.int/t/e/social_cohesion/soc-sp/Medication%20safety%20culture%20report%20E.pdf

[24] NHS National Patient Safety Agency and the Helen ***Hamlyn*** Research Centre. Information design ***for patient*** safety. Design guidance for packaging prescription medicines: secondary packaging (all types) and primary packaging (blister packs only). London 2005
http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CCYQFjAA&url=http%3A%2F%2Fwww.npsa.nhs.uk%2FEasysiteWeb%2Fgetresource.axd%3FAssetID%3D1257%26type%3DFull%26servicetype%3DAttachment&ei=_o1kVdacKIH_Up6fqJgO&usg=AFQjCNE7Q_q8xKUgK7mbLtkHgsvXBSp-dA

[25] Safety considerations for container labels and carton labelling design to minimise medication errors (draft guidance)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

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		used both for CAPs and NAPs?	
39	616-624	The information included here refers mostly to the colour-coding, which may imply that the guidance actually encourage the use of it. The examples could be used when defining the concept of colour coding and always specifying that the use is not recommended or should be limited.	
39	634-635	The acceptability of pictures, pictograms or diagrams as part of the product information of non-prescription products should always be assessed.	"… if there are any concerns. The acceptability of those should always be assessed".
39	636-637	The QRD recommendations on pack design and labelling for centralised non-prescription products is actually a **draft version**, which still may be subject to changes. It would not be appropriate to have it as a reference for industry.	To delete ~~"The QRD recommendations on pack design and labelling for centralised non-prescription products19 summarises basic principles".~~
39	664-670	Consider adding the text:	• Prescribing generically should only take place where appropriate. Some preparations must be prescribed by brand. Examples include: Ciclosporin. • The patient's intolerances and allergies must be established and taken into consideration when prescribing. • Measures should be taken during prescribing to reduce the risks associated with polypharmacy. • Appropriate dose adjustments should take place to reduce the risk of adverse drug reactions. • Evidence-based loading protocols should be used where appropriate, for example, when initiating warfarin. • The dosage should be calculated correctly. • The time of administration, where clinically important, should be correctly stated on the prescription.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
			• The quantity stated on the prescription, and the duration of therapy should be clinically appropriate. • Cautions and contraindications, based on an accurate medical history, should be considered during prescribing. • Drug interactions should be checked during prescribing and the risks managed appropriately. • Prescriptions for controlled drugs should include the appropriate information.
39	667-670		Consider including 'publications such as the BNF.'
39	674		Consider including 'publications such as the BNF.'
39	687-708	Original pack dispensing is preferred where appropriate. Some formulations are not appropriate to be included in compliance aids such as dosette boxes due to instability. Appropriate counselling should take place. Where appropriate, the delivery device supplied with the product should be used (for administration of oral liquids from multidose containers).	
39	854-858	In particular, dexterity problems can lead to inappropriate administration of inhaled products.	
39	879	New medicines should be: • Communicated to the patient, carers, GP, community pharmacy, keyworkers, outpatient monitoring clinic, care home as appropriate to maintain appropriate supply and monitoring; • Appropriate counselling should take place on the new and existing medicines; • Medication stopped during the admission should be clearly communicated to the patient, carers, GP, community	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		pharmacy, outpatient monitoring clinic, care home as appropriate to include reasons for stopping; • Appropriate outpatient follow-up relating to medicines should be arranged on discharge.	
39	881	The readability guideline has been issued by the European Commission.	"…, the European Commission has issued guidance on the readability of the labelling and package leaflet of medicinal products for human use[27]"
39	1053	Suggestion to add: …with and enteric coating **or controlled release coating**)…	
39	1079-1084	Risk of incorrect storage, for example, not storing antibiotic suspensions in the fridge and discarding the preparation after the appropriate time.	
39	1095-1098	Pyrexia can increase exposure to the active ingredient in transdermal patches. Transdermal patches containing opioids should not be used during adjustment of dosage.	
39	1105	Patches with different modified release rates may cause medication errors by the name-setting "INN + MAH", which makes it more difficult to distinguish the different products.	
40	1307	Educational material and/or SPC should when relevant include calculation for tablets in which dose is calculated from mg per weight or per Body surface or per renal function into actual dose. This is particular relevant for pediatrics and for orphan drugs.	Do not use strengths. The initiative on this guide is indeed welcome, since medication errors is a major problem globally- including EU. The guide is carefully prepared and includes a lot of relevant information for MAH and authorities. Annex 2 could be added with the following information: that can easily be mixed up ie 12,5 mg vs 125 mg 1 mg vs 10 mg, 2 mg vs 20 mg. Use numbers that differ more ie 3 mg vs 20 mg, 2 mg vs 10 mg etc. Establish agreement among companies on color coding for

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			particular forms or medications dealing with the same disease – for the safety of the patient. Point out clearly in the SPC when particular errors are known to have caused serious harm. For instance methotrexate causes serious harm if given daily for two weeks.
40	1292	Instructions for calculating when robots are dispensing should be part of SPC. This has to do with how the whole bottle content is expressed – is it the actual content or is it the content that can be extracted from the bottle (assuming some medication is left behind). This has caused a major incident in Denmark. Comments on good practice guide on recording etc of medication errors The initiative on this guide is indeed welcome, since medication errors is a major problem globally- including EU. The guide is carefully prepared and includes a lot of relevant information for MAH and authorities. Off label is not considered a medication error. We have had several off label incidents in Denmark and they end up in our reporting system – because there is nowhere else to report them. In the paragraph where off label is rejected as a medication error- I suggest that EMA procedure for off label problems is described.	
40	401	The guide writes that MAH should learn from errors which come to their knowledge – but it does not write anything about how MAH should try to find those error reports. The national authorities should forward all reports (after anonymisation) to the companies, when they can be identified. For generics or other situations where	

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		MAH cannot be identified the national authorities should publish anonymous trends for the use of the MAHs. This is important for the staff and patients who report- to know that the reports will be used	
40	328	Root cause analysis. The results using this type of analysis are debated. Use patient safety analyses instead and add a paragraph on learning from the good apple (Eric Holnagel).	
40	1066	The role of PRAC. Since medication errors are a problem the same magnitude as other adverse reactions it is suggested that PRAC includes members with this expertise. The same goes for EMA staff end staff in national authorities	
40	547	The Eudravigilence coding on medication errors should be revisited and amended to European work flows. Table 2. Extremely relevant. Comments on risk minimization strategy for insulin. The guide is indeed welcomed. Only few additional proposals Table3 The table should include focus on the long term storage (cold) of insulin products at patients´ home	
40	99	The guide should consider the eventual use of (high strength) insulin in hypo kaliemia. Use of insulin without additional glucose has caused deaths in EU. The guide should taking into consideration that patients in hospitals and nursing homes have name labels on their pens – hiding part of the color coding.	

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		The MAHs should agree on suffixes and color codes to indicate mix/long term etc.	
40	147	The abbreviation should be explained.	
40	228	It is therefore recommended to use the original packing as early as possible in the assessment, so problems with confusion or mix-up may be detected as early as possible.	
40	284	Failure to monitoring. Fx failure monitoring INR or lack of response to increased INR (Warfarin) resulting in readmissions. We have seven serious incidents in the Danish Patient Safety Database. We also see major problems around heparin bridging in anti-coagulated patients. As fx failure to represcribe after pause or lack of other antithrombotic therapy in pause. Beside bleeding incidents and readmissions we also have four deaths. We have four cases where the prescriber did not take serum conc. of gentamicin into account, thereby overdose of gentamicin resulting in kidney damage	
40	295	We have problems with Oxycodon hydrochlorid. Which is available both as release tablets and as faster-acting capsules. Both pharmaceutical forms can be purchased under the name of Oxycodone hydrochloride and is mixed-up both in the prescribing- and dispensing stage.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		In October 2014 we announced the problem in the newsletter of the Danish Patient Safety Database	
40	318	The existence of dispensing in the home care and nursing homes is not mentioned in this document. In a Danish study of serious adverse events it was found that dispensing errors most often was related to; -Wrong dose -Wrong strength / volume -Not dispensed / missing -Wrong time / frequency Analgesic drugs are by far the most common group of drugs involved in the reported adverse events.	
40	335	The problems concerning discharging and admission should have more space in the document as it is a big problem. Perhaps a separate section. See fx : Ann Pharmacother. 2012 Apr;46(4):484-94. doi: 10.1345/aph.1Q594. Epub 2012 Mar 13. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. Cornu P1, Steurbaut S, Leysen T, De Baere E, Ligneel C, Mets T, Dupont AG BMC Clin Pharmacol. 2012 Apr 3;12:9. doi: 10.1186/1472-6904-12-9.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		Errors in medication history at hospital admission: prevalence and predicting factors. Hellström LM1, Bondesson Å, Höglund P, Eriksson T..	
40	337	Most of the medication errors in The Danish Patient Database are administration errors. Administration could perhaps have a separate section. In a Danish report on adverse event in home care and nursing home it was found that the problem most often related to: - Medicine not given - Medicine not taken by patient - Medicine given the wrong time - Medicine given to the wrong patient	
40	338	One could also mention wrong infusion time. Fx: The infusion of Fentanyl run in at a rate of 40 ml / hr and not as planned 4 ml / hour.	
40	361		Confusion of units should be mentioned. Fx: Confusion between mg and mL. 5 mg of morphine was prescribed. The strength was 20 mg / ml. Instead of 5 mg, 5 ml was given, corresponding to 100 mg of Confusing i.e. and g. 3 g penicillin 6 times a day was prescribed. Instead there was dispensed 3 million. i.e. 6 times a day.

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
40	399	In the Danish report on home care and nursing home it was also found that Patches is a pharmaceutical form which gives rise to some adverse events. The problem is most often:- the patch is not be switched to the prescribed time, - the wrong strength is dispensed - old patch is not removed	
40	402	An analysis of data in the Danish Patient Safety Database found that events with insulin, both in the hospital sector and the primary care sector, frequently happen in administration. The common problems are; - wrong dose of insulin - insulin is not given - the wrong insulin is given. Some events point to some form of association as the cause of errors dosage. In some incidents 6 IU becomes 60 IU, and in one event "Novo Mix ® 30" becomes 30 IU. The most common risk situations that could be identified as a contributing factor to wrong dose is; - Missing or misunderstood communications around the administration of insulin - Monitoring of blood glucose - Mixing and infusion of insulin. By far the most common cause of a patient's wrong insulin is that the patient has more the one type of insulin with different times of action, which confuses. Of the risk situations that could be identified as contributing factors to the wrong medicament, are the most common; - the patient is using more insulin formulations and these are side by side in the same medicine box- unused / discontinued insulin have not been removed from the patient's medication.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
40	544	The group is assessing the degree of orthographic and/or phonetic similarity and the risk of cognitive error in the suggested name compared with already approved names. Taking into account in the assessment is the setting of use and elements that may increase or reduce the risk of confusion such as fx Strength and Ph. form. The potential for harm in case of accidental mix-up is also a part of the assessment.	
40	549	AGAIN: It is therefore recommended to use the original packing as early as possible in the risk assessment, so problems with confusion or mixup may be detected as early as possible.	
40	607	As in the case of Oxycodon hydrochlorid. A clear emphasize on pharmaceutical forms. A good example is MTX: Oral Methotrexate – Review on potential fatal overdose due to medication errors Final SmPC and PL wording agreed by the PhVWP in December 2011 SUMMARY OF PRODUCT CHARACTERISTICS SmPC Section 4.2: • This medicine should be taken once a week. • The prescriber may specify the day of intake on the prescription. SmPC Section 4.4: • The prescriber may specify the day of intake on the prescription.	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
		• Patients should be aware of importance of adhering to the once weekly intakes. SmPC Section 4.9: • Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported. In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions. PACKAGE LEAFLET • Take <product> once a week. Packaging and container's label/cap: • Take the prescribed dose once a week for products with an indication in rheumatology and/or dermatology only.	
40	613	In Denmark we have had several mix-ups with - Gardasil and MMR vaccination because of packaging being similar	
40	658	Health professionals in nursing home and home care are missing. And nursing are also dispensing in Danish hospitals	
40	658	The communication between health professional (and between sectors) and health professional and patient is also important - communication is a major cause to errors. Fx see note on page 13.	
40	743	In Denmark it is mandatory to report adverse events. Please see; http://ec.europa.eu/health/patient_safety/docs/guidelines_psqcwg_reporting_learningsystems_en.pdf	

Stake-holder no.	Line no.	Stakeholder comments	Proposed change by stakeholder, if any
40	745	In Denmark 'no-harm' incidents are also collected.	
40	792	Patients with impaired kidney or liver function is missing. We have had two deaths with Pradaxa because the patient's kidney function was not considered.	
40	846	And often moves between sectors because of admission and discharge.	
40	1095	We have events where elderly dementia patients have taken off the patch and chewed on it.	
40	1202	You could have a Annex 3 on packaging design?	
40	1233	Or not take the capsules out of the original package before use - Pradaxa	
40	1246	We had to make a warning stating that Patches with opioids should not be cut! This was because of an incident concerned a patient, which was prescribed a Fentanyl pain patch of 6 micrograms per. hour. Fentanyl pain patches are not available on 6 micrograms per. hour. Instead, a pain patch of 12 micrograms per. hour was cut in half before application to the skin.	
40	1307	Educational material and/or SPC should when relevant include calculation tablets in which dose is calculated from mg per weight or per Body surface or per renal function into actual dose. This is particular relevant for pediatrics and for orphan drugs.	Do not use strengths. The initiative on this guide is indeed welcome, since medication errors is a major problem globally- including EU. The guide is carefully prepared and includes a lot of relevant information for MAH and authorities. Annex 2 could be added with the following information: that can easily be mixed up ie 12,5 mg vs 125 mg 1 mg vs 10 mg, 2 mg vs 20 mg. Use numbers that differ more ie 3

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			mg vs 20 mg, 2 mg vs 10 mg etc. Establish agreement among companies on color coding for particular forms or medications dealing with the same disease – for the safety of the patient. Point out clearly in the SPC when particular errors are known to have caused serious harm. For instance methotrexate causes serious harm if given daily for two weeks.
40	1292	Instructions for calculating when robots are dispensing should be part of SPC. This has to do with how the whole bottle content is expressed – is it the actual content or is it the content, that can be extracted from the bottle (assuming some medication is left behind). This has caused a major incident in Denmark. Comments on good practice guide on recording etc. of medication errors The initiative on this guide is indeed welcome, since medication errors is a major problem globally- including EU. The guide is carefully prepared and includes a lot of relevant information for MAH and authorities. Off label is not considered a medication error. We have had several off label incidents in Denmark and they end up in our reporting system – because there is no where else to report them. In the paragraph where off label is rejected as a medication error- I suggest that EMA procedure for off label problems is described.	
40	401	The guide writes that MAH should learn from errors which come to their knowledge – but it does not write anything about how MAH should try to find those error reports. The national authorities should forward all reports (after anonymisation) to the companies,	

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		when they can be identified. For generics or other situations where MAH cannot be identified the national authorities should publish anonymous trends for the use of the MAHs. This is important for the staff and patients who report- to know that the reports will be used	
40	328	Root cause analysis. The results using this type of analysis are debated. Use patient safety analyses instead and add a paragraph on learning from the good apple (Eric Holnagel).	
42	300-305	Since only the INN pramipexole is stated, Boehringer Ingelheim kindly asks to clarify whether this example refers to Sifrol/Mirapexin, or to experience gained from generic pramipexole. In case experience gained from Sifrol/Mirapexin is being described, the MAH of Sifrol/Mirapexin, Boehringer Ingelheim International GmbH (BI), is concerned about the way information is being presented implying a causal relationship which seems to be incorrect. Provision of wording in the SmPC and Package Leaflet stating to not chew, divide or crush the prolonged-release tablets and to swallow the prolonged-release tablet whole was **not triggered** by reports about accidental overdose, when Sifrol/Mirapexin prolonged-release tablets were crushed for ease of swallowing. Such warning statement was already contained in the initial submission of line the extension application EMEA/H/C/133,134/X/51. Furthermore, BI is not aware about any cases of overdose due to crushing of Sifrol/Mirapexin prolonged-release tablets. In case the Agency has additional information which BI is not aware of, BI would be interested in learning more about such potential cases.	Unless the example originates from generic pramipexole or EMA holds additional information, which BI is not aware of, it is kindly requested that the pramipexole example is deleted from or appropriately revised in the draft guideline.

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		Likewise, redesign of the outer packaging for better differentiation between the two formulations was **not triggered** by reports about incorrect dosing with Sifrol/Mirapexin when the immediate-release formulation was mistaken for the prolonged-release formulation. The **theoretical risk** for dosing error (3 times versus once daily intake of the prolonged-release formulation) was intensively discussed during line extension procedure EMEA/H/C/133,134/X/51,59 and led to revision of the main colour scheme of the outer packaging design to better differentiate between the two formulations. Additionally, in that same procedure the statement “once daily” in red colour was prominently added to the outer packaging of the prolonged-release formulation.	
42	306-316	The errors described here are not preventable by action on the part of the MAH.	There is a need to highlight this problem to prescribers. National competent authorities communicate the nature and scale of this problem to prescribers in order to address errors that are beyond the influence of MAHs.
42	318 -335	As above	How will some of the errors in this section be communicated to prescribers? How will action be taken?
42	530	“Frusemide”	Correction to “furosemide”
42	531-533	BI is aware about name confusions between **Pradax** and Plavix in Canada before 2013, and has also reported these to the EMA in the PSUR and RMP: • During the initial submission of Pradaxa in Canada, Health Canada did not accept the BI proposed trade name Pradaxa and requested a change to Pradax, which BI accepted. • Later on, cases of name confusion between Plavix and **Pradax** were reported from the Canadian market. • As a consequence Health Canada requested BI to change	Unless the EMA has additional information, which BI is not aware of, BI kindly requests that the Pradaxa example is deleted from the draft guideline. Alternatively, the guideline could clarify that the name confusion pertained to Pradax (an outdated local Canadian trade name) and Plavix and not to Pradax**a** and Plavix.

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		the trade name from **Pradax** to **Pradaxa,** which was then implemented by BI starting in January 2013 • As imposed by Health Canada in the context of the trade name change from Pradax to Pradaxa, BI has submitted for 2 years 8 quarterly reports evaluating any medication errors world-wide caused by name confusion (calendar years 2013 and 2014). This follow up measure has now been completed with the conclusion not only for Canada but for world-wide markets, that the received data do not support an unexpected level of confusion between Pradaxa and any other drug. Based on the available data, no risk minimisation activities are considered necessary. • BI is not aware of any further name confusion cases for Pradax**a** and Plavix	