30 May 2013
EMA/CHMP/277592/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Position paper on potential medication errors in the context of benefit risk balance and risk minimisation measures' (EMA/CHMP/277591/2013)

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

Stakeholder no.	Name of organisation or individual
1.	German Pharmaceutical Industry Association (BPI), Boris Thurisch
2.	Association of the European Self-Medication Industry (AESGP), Helga Blasius
3.	Prescrire, Florence Vandevelde
4.	a.r.c. pharma, Jeanne Ducorroy
5.	NHS Commissioning Board, David Cousins
6.	Gilead Sciences International Limited, Carol Walker
7.	The Guild of Healthcare Pharmacists , Scott Savage
8.	European Industrial Pharmacists Group, Jane Nicholson
9.	European Federation of Pharmaceutical Industries and Associations (EFPIA), Isabelle Clamou
10.	Merck Sharp & Dohme (MSD), Angelika Joos
11.	Mundipharma Research GmbH & Co., Michael Sturm
12.	Health Canada, My-Yen YU

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1. General comments – overview

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1.	Generally, we are talking about medicinal products, which are subject to registration procedures. For the packaging/labelling QRD-templates have to be used. Moreover, a readability test is required. According to the EU-labelling requirement the name of the medicinal product must be followed by the strength and the administered form. These general preconditions have to be considered and the comments should be read having these pre-conditions in mind. Examples of potential benefits for products that differ from established products are given in the paper. These benefits are balanced against potential risks.	*No action taken.* *As a general remark to several of the comments listed below, it is pointed out that a number of issues have been discussed in the recent EU regulatory workshop on medication errors, which took place at the EMA from February 28 to March 1, 2013. A report on this workshop (EMA/144458/2013) is available via the EMA website (http://www.emea.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf).* *These comments will also be addressed in the context of the proposed action plan following the recommendations from the EU regulatory workshop on medication errors (http://www.emea.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/05/news_detail_001796.jsp&mid=WC0b01ac058004d5c1).*
3.	The guideline on good pharmacovigilance practices defines medication error as “any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer” (2). Pharmaceutical companies are encouraged to “take into account potential reasons for medication errors (…) during the development phase and during the design of a medicinal product for marketing”, as part of a future risk management plan, mainly taking into account the product’s: name; presentation (including its pharmaceutical form and packaging); instructions for use (including reconstitution procedures, routes of administration, dose calculations); and	*The focus of the position paper has been deliberately set on medication errors occurring due to confusion of new with authorised/established medicinal products. It is acknowledged that this does not cover all potential reasons for medication errors; however it is believed that the current proposal marks one important step in tackling this multifaceted issue and that the focus chosen allows for a meaningful approach.* *The difficulties of developing a comprehensive methodology for systematically assessing the (future) risk of confusion of*

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	labelling (2). Prescrire's analysis of the EMA's draft position paper, which was released for consultation on 1st June 2012, is based on the experience we have acquired in analysing the packaging of medicinal products (3–7), viewing it as a preliminary and welcome move by the EMA to give greater attention to the risks of medication errors. **The proposed medication error risk assessment is insufficient and limited to "copies" of existing medicines** Contrary to the implication of its main title, the EMA's draft position paper is not about consideration of the risk of medication errors as part of the evaluation of every medicinal product before market introduction (1). It focuses on the risks generated by medicinal products "containing the same active substance [as an existing medicinal product] and similar in some other attributes such as appearance and/or name but different in strength, dosing, route of administration (…) that [are] presented in a different pharmaceutical form, a new administration device or [have] a different composition or [are] intended to be used in a different patient population or indication, etc." (1). The EMA's draft position paper intends to minimise the risks associated with such "copies" and variants of existing drugs through risk management plans. **What about umbrella brands?** Umbrella brands use the same brand name extension (e.g. "Doli°", "Nuro°", "Vicks°") on a range of products with different compositions. Their dangers are well documented (a). But the EMA does not specify whether its position paper applies to	*medicinal products and the resulting implications for the benefit/risk balance of a new product is an acknowledged shortcoming. This applies for quantitatively comparing benefit and risk of a given medicinal product in general. Future effort will be necessary to address this issue. For this position paper it is considered beyond the scope, though.* *The 7 proposals made incorporate meaningful and well comprehensible ideas of how the important topic of medication errors could be addressed at large. Several ideas are already comprehensively reflected on in existing EMA guidance documents (e.g. SmPC GL), some are being covered in the present position paper. A number of them would possibly require legal amendments at different levels of decision-making and may be addressed in the context of the proposed action plan following the recommendations from the EU regulatory workshop on medication errors (EMA/144458/2013).* *In summary, we would like to iterate that the Position Paper is intended as a means to communicate the general positioning and views of the CHMP on the very specific problem of medication errors caused by confusion (as clearly delineated in the subheader of the document). It is intended to create awareness towards this issue and possible solutions rather than providing detailed guidance or instructions regarding labelling/packaging/etc. or the quantification of an identified risk.*

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	the risk of confusion between medicinal products belonging to the same umbrella brand. **No systematic assessment of potential medication errors for every medicinal product** By focusing on the particular situation where confusion could arise between products containing the same active substance, i.e. on a predictable risk of medication error, the EMA avoids applying the kind of thorough, exacting methodology required to test for and detect all the risks of medication errors associated with a given medicinal product (8). For this particular risk of confusion, the EMA proposes evaluating only the extent to which the new product differs from the existing product and the adverse effects that would ensue if an error occurred, but not the risks of error inherent to medicines that are already marketed (b). Furthermore, the EMA proposes weighing the potential benefits of the "copy" or variant of an existing medicinal product against its risks only when a "high" risk of confusion is identified. But the EMA does not propose a method for quantifying these risks. **No truly comparative assessment of risk-benefit balance** The risk-benefit balance of copies and other variants cannot be assessed unless methods are provided for quantifying expected benefits (e.g. fewer adverse effects or greater convenience) and comparing them with risks (e.g. the criticality of each type of medication error), which the EMA's draft position paper fails to do (see our proposals below). **Risk management plans: insufficient and too late to prevent**	*No action taken.*

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	medication errors The EMA has contented itself with asking that “risk management plans” be put in place, but they are produced too late and provide hardly any additional risk-prevention measures beyond those required whenever marketing authorisation (MA) or a variation is granted. These risk management plans merely involve: - strengthening alerts and warnings on the SPC, package leaflet and labelling; - and possibly, on a case-by-case basis, changing the name, testing the readability of package leaflets, and proposing different packaging designs, yet no practical evaluation is required of the effectiveness of measures to help users discriminate between the different products. **In summary** The measures the EMA is considering in order to improve the prevention of medication errors associated with copies and variants of existing medicinal products do not go much further than the information strengthening traditionally used by drug regulatory agencies and pharmaceutical companies. The EMA does not propose a method for evaluating these measures. Rather than implementing risk management plans aimed at minimising the risks of certain medicines after their market introduction, errors would be prevented more effectively by systematically and rigorously analysing the risks of medication error and taking preventive action before market introduction (see our proposals below). **Prescrire’s 7 proposals to prevent the risks of error associated with medicines and associated devices**	

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	The packaging of medicinal products (outer packs, package leaflets, blisters, child-proof caps, etc.) is a fundamental part of a drug's risk-benefit balance and a key factor in ensuring correct use and preventing medication errors. Pharmaceutical companies that design packaging and the drug regulatory agencies that grant marketing authorisations must stop overlooking packaging, given its importance to patient safety and the correct use of medicines. The poorly designed packaging of currently marketed medicines exposes patients to the risk of errors that could have been prevented. Identifying these dangers after market introduction is also more disruptive to pharmaceutical manufacturing than implementing modifications to minimise foreseeable risks before market introduction. Health authorities (c) must have the means to effectively reduce the likelihood of errors related to medicines and associated devices, without passing the risk onto users. • **Proposal 1:** **For new medicinal products, assess the potential for error associated with packaging and labelling as part of the evaluation of the MA application** In addition to evaluating the benefits and harms associated with the active substance, drug regulatory agencies must conduct a separate assessment of the risk of error associated with the medicine's packaging and labelling and publish their findings in a medication errors public assessment report, right from the earliest stages of the registration process, so that improvements can be implemented before the MA is granted (d).	

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	To enable the health authorities to produce a medication errors risk assessment, pharmaceutical companies should provide a dossier including: - an evaluation of the labelling (including the name), instructions for use, preparation and administration, and the associated devices, addressing their effectiveness in preventing medication errors in healthcare situations (cf. proposal 2 “Raise quality and safety standards for packaging”); - a prospective analysis of the risks of medication errors, to better quantify the danger to which patients might be exposed in real-life healthcare situations (cf. proposal 3 “Establish rigorous criteria and methods for assessing the risk of medication errors”). To perform this task effectively, drug regulatory agencies must strengthen their teams’ resources and expertise in packaging analysis, by creating task forces dedicated to assessing packaging-specific risks and to developing new solutions for improving packaging safety and usability. • **Proposal 2:** **Raise quality and safety standards for packaging** The EMA should take on board the many recommendations to improve packaging that have been put forward by *Prescrire* (9) and others, such as the Council of Europe (8), and in particular 7 general measures (numbered 1 to 7) and 4 measures specific to certain pharmaceutical forms (numbered 8 to 11): 1. The international nonproprietary name (INN) and dose strength must be prominently and legibly displayed on labelling and package leaflets to ensure that medicines are identified by their	

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	real name, the brand name having less prominence than the INN (application of the 2009 European Commission's guideline on the readability of the labelling and package leaflet of medicinal products for human use (Rev 1 ref. ENTR/F/2/SF/jr (2009)D/869)); 2. The essential information must be clearly displayed on at least 3 surfaces of the secondary packaging (box), leaving adequate space to systematically add patient-specific information about the treatment, either handwritten or in the form of a "dispensing label"; 3. Font sizes must be large enough to be read easily; 4. Clear descriptions of dose strength and concentration must be given; 5. All medicines whose doses are standardised must be supplied in unit dose presentations that are ready to use or administer; 6. Reject unintelligible multi-language packaging; 7. Evaluate graphics, pictograms and colours, mainly used to help users discriminate between different dose strengths of the same medicine, paying special attention to colour coding that might cause errors by providing a false sense of security; 8. Ban bulk bottles for tablets and capsules, beginning with substances that that are fatal to children (e.g. *iron*, *methotrexate*, *quinine*) and orodispersible medicines; 9. Require each dose of tablets or capsules packaged in blister	

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	packs to be individually and fully labelled, and require a safety film on blister packs that contain particularly dangerous drugs (**e**); 10. Require a child-proof cap on bottles of oral liquid medicines, unless accidental ingestion has been shown to be harmless; 11. Require multi-dose oral liquid forms to be supplied with an appropriate dosing device of suitable capacity and accuracy (such as an oral delivery syringe graduated in milligrams or units). • **Proposal 3:** **Establish rigorous criteria and methods for assessing the risk of medication errors** Several of the Council of Europe's recommendations describe the principles and methods for assessing the risk of errors associated with trade names and packaging, based on user testing by healthcare professionals and patients in real-life healthcare situations (8). The report includes a safety assessment form for this purpose, which is very similar to the one used by the Prescrire Packaging Working Group (3,4). We urge drug regulatory agencies to use it systematically and improve it. The principle of readability testing must be extended to all information on the packaging of medicinal products: the package leaflet (as already required by Directive 2001/83/EC as amended by Directive 2004/27/EC), but also the labelling on all packaging items (box, primary packaging, dosing device), including any information depicted graphically (pictograms, dosing schedules, signs and symbols). The use of any graphical information that has not been	

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	evaluated or has been deemed unsatisfactory in tests should be prohibited. Readability and user tests on packaging from the same commercial range are an effective way of detecting risks of confusion and medication error. They should be performed by an adequate number of users from the population liable to use the medicine. • **Proposal 4:** **Continue assessing the risk of medication error throughout a medicine's life** Medication errors are identified through reports sent to pharmacovigilance systems and to patient safety organisations. These data must then be published in periodic safety update reports (PSUR) (10,11). When medication errors occur, the initial medication error risk assessment report must be reviewed to improve the risk assessment criteria. Data on overdosing errors and accidental ingestion (involving both active substance and excipients) must be reported without delay in the SPC and public assessment reports (also see proposal 5). Many major variations (new indication, paediatric extension, line extensions involving new forms or dose strengths, etc.) substantially alter the context in which the drug will be used and consequently the original risk assessment. Drug regulatory agencies should therefore reassess the risk of error associated with its packaging, labelling and associated devices. Other events in the life of a medicinal product should also prompt re-analysis of both the risk of error and its packaging: - expanded distribution (when a hospital-only medicine is made	

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	available in the ambulatory sector); - reclassification of a prescription-only medicine as a self-medication product or over-the-counter (OTC) product. Worksharing procedures to reassess paediatric data on old medicines under Article 45 of the Paediatric Regulation of 2006 are an unmissable opportunity for drug regulatory agencies to ask pharmaceutical companies for practical improvements to their packaging, to improve the safety of all patients (12). • **Proposal 5:** **Improve information on packaging** • The information provided by health authorities for healthcare professionals and patients should be improved: • Packaging items should be described and instructions for their use provided in the SPC and package leaflet; • When a new marketing authorisation or major variation is granted, publicly accessible mock-ups of all of the packaging items should be published; • When a packaging item has caused errors or the potential for error clearly exists, a publicly accessible detailed analysis should be published, linked to or included in the public assessment report (EPAR, national, decentralised or mutual recognition procedure PAR) on the websites of the appropriate medicines agencies; • When changes are made to any packaging item that could affect	

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	how it is used. • **Proposal 6:** **Update existing guidelines to improve error prevention** • Several existing guidelines are inadequate and need to be refocused, particularly with regard to: • Recommendations on brand names, which defend trade names at the expense of use of the INN; the focus of these recommendation must be shifted towards patient safety (**f**) (13); • Recommendations on the expression of dose strength and concentration in the name of medicinal products exist solely for administrative purposes, to discriminate between the various MA dossiers of the same product line; these recommendations must be revised to prevent errors associated with the coexistence of different dose strengths and concentrations and to help patients and healthcare professionals use medicines correctly (14); • Recommendations on self-medication products; these recommendations must ensure patient safety by improving the packaging and labelling of self-medication products (**g**) (15). • **Proposal 7:** **Increase the attention given to the prevention of medication errors in all drug regulatory agency activities** In addition to product-specific risks, drug regulatory agencies can avert other sources of error through vigilance and by paying constant	

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	attention to the prevention of medication errors, such as foreseeing off-label use. If the rules on the use of INNs had been applied: the error in the expression of dose for eribulin (standardised at 1 mg/2 ml of eribulin mesilate instead of eribulin base) would have been corrected at the clinical trial stage (16); modified INNs would have been requested for lipid formulations of amphotericin B or daunorubicin (17); and inappropriate use of brand names in SPCs, such as that of Rasilez°, would have been avoided; etc. A priority in the non-prescription or over-the-counter (OTC) sector is to improve the information about pregnancy in the package leaflets of NSAIDs. The data on NSAIDs suggest that their administration during the first trimester of pregnancy increases the risks of miscarriage and malformations. If they are taken after the first trimester, NSAIDs expose the fetus to serious and sometimes fatal cardiovascular and renal risks. However, in some French package leaflets examined in 2011, regardless of dosage form and legal status, NSAIDs were only clearly contraindicated from the sixth month of pregnancy (7). **Notes:** a- The packaging of medicines of "umbrella" brands are designed to be easily recognised by users as belonging to the same brand. Their graphics make very different medicines look alike, even though they may contain different active substances, with the potential for confusion and medication errors. b- European and national competent authorities do not publish exhaustive lists of all the medicinal products that are currently authorised in the European Union, nor their summaries of product	

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	characteristics (SPCs) and package leaflets. Under these conditions, a comparison with the existing product hardly seems possible. c- European Commission, European Medicines Agency, Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh), European Directorate for the Quality of Medicines (EDQM) of the Council of Europe. d- The MA dossier would therefore include a medication errors assessment report, in addition to the clinical assessment report and the safety assessment report. e- A small device could be included in the box to help patients with limited dexterity remove tablets or capsules from the secure blister pockets. f- To achieve this, the EMA must: - publish the list of drug names known to have generated confusion; - facilitate the reporting by healthcare professionals and patients of drug name-related errors; - adopt and publish a method for assessing the risk of confusion before marketing authorisation is granted; - abandon brand name extensions, whereby medicines with different compositions that belong to the same “umbrella” brand have almost the same name (i.e. Nuro something°) which is confusing; - adopt stricter standards for the naming of fixed-dose combinations; - revert to more prudent use of abbreviations and suffixes, which cause confusion; - involve patients in the search for improvement (ref. 18,19). g- For self-medication products, it is necessary to: - stop accepting umbrella brand name extensions, which cause confusion and serious medication errors;	

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	- review the rules on the use of colour on the packaging of medicinal products, taking into account the impact of colour perception defects, which affect a significant proportion of the population; - organise how information for patients is divided among the package leaflets and the secondary packaging (including the inside of the box) and how the most important information is highlighted; etc. (ref. 15). • Poor packaging is a major cause of medication errors. In its response to the European Medicines Agency's public consultation on potential medication errors in the context of benefit risk balance and risk minimisation measures (1), Prescrire calls for the safety and usability of the packaging and labelling of new medicines to be assessed as part of the evaluation of marketing applications. Prescrire calls also for a re-examination of all the packaging of existing medicinal products. **Summary:** • The draft position paper that the European Medicines Agency (EMA) released for consultation on 1st June 2012 is not about considering potential medication errors as part of the evaluation of all medicinal products before marketing authorisation is granted. It focuses on the risks generated by copies containing the same active substance as a medicinal product that is already marketed. The draft does not specify whether "umbrella" brands fall under the scope of this position paper, despite their dangers. • The identification of potential medication errors should result in measures to prevent their occurrence. Yet the EMA simply asks that a "risk management plan" be put in place, providing hardly	

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	any additional risk-prevention measures beyond those required whenever marketing authorisation (MA) or a variation is granted. • *Prescrire*'s response to the EMA consultation details several concrete proposals that should enable health authorities to effectively reduce the risk of errors associated with medicines and related devices. *Prescrire*'s two main proposals in order to effectively prevent preventable medication errors are that: o the safety and usability of the packaging and labelling of new medicines must be assessed as part of the evaluation of MA applications. Drug regulatory agencies must conduct this assessment and publish the results in a "medication errors public assessment report" well before the medicinal product is marketed; o European authorities and national medicines agencies must re-examine existing medicinal products since the packaging of medicinal products is too often poorly designed and conducive to errors. They should begin with packaging items most frequently implicated in medication errors. They should also use various opportunities throughout the medicinal product's life (when examining applications for a major MA variation, in case of expanded distribution (when a hospital-only medicine is made available in the ambulatory sector), on reclassification, or during worksharing procedures to assess paediatric data under Article 45 of the Paediatric Regulation of 2006).	
4.	I have just a comment regarding the Position paper on potential medication errors in the context of benefit-risk balance and risk minimisation measures. It seems to me that a clear/detailed definition of what is a medication error would be necessary in the scope of the position paper. I note that medication errors related to administration are mentioned in the draft document, but not errors	*A definition of medication errors addressed in the Position Paper is provided in paragraph 4 of the introduction.* *While it is agreed that the potential for error may arise at each step of prescription/delivery/administration, these steps ought to be understood as a joint concept referable to*

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	related to prescribing or delivery. Should they be assessed in the context of the risk management plan when introducing a new form / indication?	*as "therapy", "treatment" or "administration" in a broader sense. The term "administration" used throughout the document refers to this broad concept where appropriate, depending on the specific context.* *No action taken.*
5.	The title of the position paper does not clearly describe the topic. We suggest the following title: Position paper on potential medication errors arising from variations, extensions and different indications of existing products, in the context of balancing benefits and risks We welcome greater consideration of practice risk in use issues by pharmaceutical manufacturers and regulators for all Marketing Authorisation applications, variations and extensions. We are disappointed that very few risk management plans for new medicines appear to consider or include risk minimisation measures concerning wrong drug, dose, formulation, route, preparation and administration issues. With the recent change in the EU directive on Pharmacovigilence requiring greater consideration of medication errors requiring expertise in patient safety, human factor and design, we are concerned that staff currently working in pharmacovigilence in the industry and regulators have insufficient knowledge and experience of these issues. Urgent action is required to correct this in order for initiatives described in the The title of the position paper does not clearly describe the topic. We suggest the following title: Position paper on potential medication errors arising from variations, extensions and different indications of existing products, in the context of balancing benefits and risks	*The proposed alternative title is not agreed as it would, for example, exclude new applications (e.g. of generics with an additional strength).* *No action taken.*

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	We welcome greater consideration of practice risk in use issues by pharmaceutical manufacturers and regulators for all Marketing Authorisation applications, variations and extensions. We are disappointed that very few risk management plans for new medicines appear to consider or include risk minimisation measures concerning wrong drug, dose, formulation, route, preparation and administration risk issues likely to arise in practice. With the recent change in the EU directive on Pharmacovigilence requiring greater consideration of medication errors requiring expertise in patient safety, human factor and design, we are concerned that staff currently working in pharmacovigilence in the industry and regulators have insufficient knowledge and experience of these issues. Urgent action is required to correct this in order for initiatives described in the New directive and in this position statement to be effective in minimising practical in use risks with medicines in practice. The EMA and the Commission on Human Medicines should seek to strengthen their knowledge and expertise in patient safety by seeking additional assistance from topic experts and to develop training courses and materials to promote this knowledge within the EMA, National Pharmacovigilance centre and the Industry. The WHO Uppsala Monitoring Centre in Sweden is just completing aN EC funded project on Managing Medicines that includes the publication of 'Guidance for Pharmacovigilance Centres On Reporting and Learning Systems for Medication Errors'. This material will be of assistance to the EMA position on medication errors. There are a number of governmental and non-governmental patient safety organisations in Europe that collect information concerning	

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	medication errors and provide safe medication practice guidance. It would be helpful if the role of these organisations was recognised in the guidance. These organisations can provide information concerning medication error incidents and practical safe medication guidance to regulators, industry and healthcare providers	
6.	It is not clear why this position paper is specifically needed for products with the same active substance. The risk for medication errors has to be assessed within the Risk Management Plan (RMP) and every new product must have an RMP. The considerations cited do not differ as the consequences remain the same, whether underdosing or overdosing and whether there is impact on efficacy or if the incorrect population is exposed. The benefits cited will vary according to the nature of errors and if certain changes are feasible excipients may need to be the same, and pack sizing too. If there is any benefit to this paper it would be as an attachment to the RMP GVP module rather than as a stand-alone paper.	*Irrespective of the consequences of a medication error, one specific cause is addressed in the Position Paper. Therefore, the focus on confusion of new with authorised/established medicinal products at the same time mandates the need to concentrate on products with the "same" active substance.* *No action taken.*
7.	The Guild of Healthcare Pharmacists generally supports the position paper as it aims to improve medication safety and reduce confusion of products with the same active substance but having different aspects. These issues are often overlooked when such products are introduced. There appears to be a heavy reliance on direct interaction between healthcare practitioner and pharmaceutical company, which may not necessarily be permitted by some organisations or individuals. Alternative measures must be considered in such cases. There needs to be clear distinction between the need for a new proposed product and an unnecessary and costly license extension.	*The discussion whether a line extension is worthwhile is considered beyond the scope of the Position Paper. If the added benefit balances negatively against added risks (including the risk of confusion as addressed in the paper) this will affect the decision about market approval.* *No specification taking into account OTC or prescription-only character of medicinal products considered necessary. The same principles of B/R assessment are followed in either case.*

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	The pharmaceutical industry may be seen as deliberately altering existing product properties to gain longer market share for little perceived clinical benefit. The pharmaceutical industry should clearly explain the absolute or relative clinical benefit and the associated patient safety risks and confusion. An example could be extended release formulations when pharmacokinetic data suggests little benefit. Also there is no mention if this consultation is specific for prescription only medicines. 'Over the counter' (OTC) preparations should also have similar safety measures applied. One further point to note is the use of a well-established OTC brand name with many different medicine additions (eg adding a further analgesic) or formulation changes (to allow "soluble", "rapid", "faster mode of action"), and how this may confuse the general public when they may intend to purchase the product they may have previously used, now being confronted with an array of different brand name options. Clarity and consistency is urgently required to avoid such confusion.	*No action taken.*
8.	Apart from the minor amendments shown below, we fully agree with and support the proposals of the European Medicines Agency. We consider the document should minimise potential medication errors	*No action taken.*
9.	EFPIA welcomes the opportunity to comment upon this position paper, taking into account its relevance in the context of the new Pharmacovigilance legislation. We see the publication of this document as a positive step for the reflection on practical aspects of how MAH should consider the potential risks related to specific formulations or new methods of administration of medicines.	*No action taken.*
9.	We also note that one of the problems currently faced by MAH is the	*While this issue is acknowledged in principle, a legal debate*

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	existing statutory framework on invented names, which links a new trademark to a new MA, and similarly prohibits the use of the same trademark for two different MAs. Because of this requirement, one important tool in minimizing risk related to the introduction of a new formulation/indication – the naming strategy – is pre-determined. The legislation requires that the same invented name be used for a line extension, and does not allow the use of a different invented name. This can be limiting to applicants when planning to address the risks under discussion. For example a line extension for a long-acting release product cannot be identified as such in the product name with a suffix e.g. Depot or LAR appended to the invented name, as use of a suffix requires the filing of a completely new MAA. We would ask that there be some flexibility in the strict rules allow different formulations of a product under the same MAA to be labelled and packaged with names that are helpful and communicative to prescribers, patients and carers, and address the risks identified in the paper.	*about the conflict between benefits of brand recognition and the associated risk of confusion caused by naming provisions lies beyond the scope of the paper.* *No action taken.*
9.	We also feel that while the use of the EDQM Standard Terms goes towards some standardisation across the EU, patients and HCPs could benefit from further standardisation for different formulations via the use of symbols, colours, words or other identifiers, e.g. paediatric, injectable, infusion, oral, oral modified-release, auto-injector, patch etc. While attempts to agree on those have not been successful in the past (e.g. for a paediatric symbol), the search for standardised qualifiers acceptable in all countries should continue as they can be a factor in improving safety in a harmonised way.	*Agreed in principle. The identification of standard qualifiers/terms lies beyond the scope of the paper, though.* *No action taken.*
9.	We note the document is written in context of small molecule/ drugs.	*While biologicals have not been formally excluded from the*

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	Medication error with vaccines and biologicals should also be considered within the scope of the position paper. In addition it has been recognised that, for effective pharmacovigilance of biologicals, traceability to the brand level is necessary. This contrasts with pharmacovigilance for small molecule products, where traceability to the INN level is usually sufficient. The EMA and several national regulatory authorities have issued notices to this effect. Moreover, Article 102 of Directive 2010/84/EU states that Member States shall ensure that any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report should be identified by the name of the medicinal product and the batch number. Therefore, the labelling for biologics should contain directions to ensure that this information is recorded in the patient record.	*rather generic scope of the paper, it is acknowledged that some of the specific issues touched upon will not necessarily be applicable for chemicals and biologicals to the same extent. That being said, we believe that the reflection on B/R assessment based on the potential for medication errors should be done irrespective of the nature of the medicinal product concerned. The scope of the paper therefore includes all types of medicinal products. To clarify this, the wording of the first sentence of the second paragraph of the introduction has been slightly amended.* *Specific issues regarding the labelling of biologicals and traceability are beyond the scope of this paper.*
9.	However, this position paper only considers the measures to be taken when introducing changes within a product range. It is also necessary to look at the risk of medication errors when introducing a new product to the market, and EFPIA would welcome a position paper to discuss how this could be done.	*The introduction of new products to the market has not been excluded from the scope (please see lines 29-32).* *No action taken.*
10.	Paper should highlight that the contents and recommendations would not apply in the situation where a "new product" (with same API as an established product) has entered the market but replaces the established product on the market.	*Not applicable. (Please see previous comment.)* *No action taken.*
10.	The document is written in context of small molecule/ drugs. Recommend expansion of scope to include text/reference or examples in various sections —especially section 1,2,3-- to vaccines	*Please see related comment on page 21/22 of this document.*

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	and biologicals in document, such as new multivalent vaccines, benefit there to enhance compliance, decrease dosing etc; reduced antigen concentration to decrease AEs from vaccines/biologicals; needleless technology to reduce pain; formulation switch to allow for SQ administration rather than IM dosing.	
10.	It is not clear how this paper aligns with the EMA/CHMP guidance on risk/benefit assessment/quantification.	*This Position Paper addresses one specific source of risk and should therefore be read in context of the general guidance on B/R assessment.* *No action taken.*
11.	We have one general comment about the document header. That comment does appear as the first of our two specific comments below.	*No action taken.*
12.	There is a need for more consistent terminology and definitions. The following terms are used throughout the document to indicate a reference product: existing product, reference product, already established product, already authorised product, established product, product established in clinical use, existing medicinal product, original product. Terms should be clearly defined at the beginning of the document, and then used consistently throughout to improve the clarity of language and meaning for the reader. The lack of proper terminology may engender confusion as to the scope of products addressed. There are references in the paper to product reformulations containing the same active substance and also to reformulations containing similar active substances. The term similar should perhaps be used throughout the document in order to define	*This is acknowledged. While it is difficult to find a generic term that accurately describes the covered scenarios without having a specific but misleading connotation in drugs regulation, the term "authorised/established" has now been introduced to uniformly replace the various definitions used in the previous version of the document.*

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	the scope beyond product line extensions to capture all product reformulations. Key themes prevalent in patient safety should be emphasized. There exists a widespread recognition in the patient safety community that medication errors are preventable and occur as a result of a complex interplay between people, processes, systems and equipment. The document however states that errors may be "attributable primarily to …the user" and that "in many cases a combination of unfavourable circumstances will be the cause." This suggests a random or arbitrary element to medication errors that would seem to minimize the importance of preventative action such as ensuring differences between products are clearly identified on the label.	*The document does not state that errors are primarily attributable to the user. This is a misinterpretation. It states that there might be one primary cause (be it user [incl. professionals] or the product due to its characteristics). In most cases though, several components contribute to a mistake being made. Also, the importance of preventive action (through anticipation and minimization of risk) is the key message of the document.* *No action taken.*

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
8-10	2.	Comment: The subtitle refers to products with a similar INN; however the scope of the document only includes those with the same INN. Proposed change (if any): Focus on medication errors caused by confusion of a newly introduced medicinal product with an existing one, with the same active substance but different in some aspects	*Accepted.*
8-10	11.	Comment: The subtitle refers to products with a similar INN, however the scope of the document only includes those with the same INN. Proposed change (if any): Focus on medication errors caused by confusion of a newly introduced medicinal product with an existing one, ~~similar in~~ *with the same* active substance but different in some aspects.	*Accepted.* *See previous comment.*
9,19,31	12.	Comment: There is a lack of consistency with terms used to describe the scope of products covered by the paper. Line 9 identifies products *similar* in active substance. Later (lines 19, 31) the phrase “the same active ingredient” is used. The same active ingredient	*Not accepted.* *Please see previous two comments.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		suggests product line extensions; the term similar suggests all reformulations. Proposed change (if any): Consider the use of the phrase 'containing a similar substance' in place of 'the same active.'	
9,13,30,37	12.	Comment: A variety of terms are used throughout the paper to suggest a reference product, eg. already authorised product, already established product etc. Proposed change (if any): Define the term 'reference product' and use consistently throughout the paper	*Partly accepted.* *The term "authorised/established" has now been introduced to uniformly replace the various definitions used in the previous version of the document. Please also see the last comment on page 23 of this document.*
11	12.	Comment: The phrasing can be improved for greater clarity. "Changes may be introduced" could refer to changes in prescribing patterns rather than to the product itself. Proposed change (if any): During the life-cycle of a medicinal product, changes to the product may be introduced that can have an impact on its use in clinical practice.	*Accepted.*
13, 146, 53	12.	Comment: Define acronyms the first time they appear in a paper.	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
13-15	12.	Comment: 'Extensions of indications' and 'different indication' are repetitive. Proposed change (if any):	*Accepted.*
14	12.	Comment: For purposes of readability, omit phrase "as well as a different" Proposed change (if any):	*Accepted.*
15-17	12.	Comment: The last sentence of this paragraph seems to repeat the ideas already expressed in lines 11 to 15. Proposed change (if any): Remove the last sentence of the first paragraph.	*Not accepted.* *The last sentence refers to the introduction of new products whereas the previous lines refer to changes to authorised products.*
18-22	12.	Comment: The introduction of all new products bears a potential risk of medication errors. What needs to be highlighted is that the introduction of these altered products bears a potential risk of *confusion* with the reference product. Proposed change (if any): "bears a potential risk of confusion with the reference products. The assessment of such changes should include a	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		comparison with existing products on the market in view of the potential risk of medication errors caused by this confusion."	
20-22	7.	Comment: It would be helpful to include an example of different forms being confused when prescribed, dispensed or administered Proposed change (if any): To consider an example	*Not accepted.* *Not considered useful in this rather general paragraph.*
23-26	12.	Comment: In the patient safety community, medication errors are considered to be multi-factorial in etiology. They are rarely attributable to a single user and instead are considered to be the result of a complex interplay between equipment, processes, products and people. The use of the term 'unfavourable circumstances' suggests a randomness to the occurrence of medication errors. Patient safety experts advocate that errors occur as a result of specific elements in medication use systems that, if unchanged, will lead to repeat errors. Proposed change (if any): This paragraph should instead emphasize the importance of ensuring that new products are named/labelled/packaged/marketed to optimize safe use and prevent medication errors.	*Partly accepted.* *Added "yet preventable" before "circumstances.* *This paragraph is introductory in nature. Preventive measures are discussed in much more detail later on. Also, product-related shortcomings and users' mistakes cannot be considered separately.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
36-37	12.	Comment: Lines 29-32 and 36-37 are repetitive. Proposed change (if any):	*Accepted.* *No action taken. Does not hamper readability.*
36-46	9.	Comment: For clarity, it is recommended that the potential causes and types of medication errors are grouped. Proposal (if any): Suggested causes and types are: <u>Causes of Medication Errors</u> • Identification – Failure to identify which product to use, possible error caused by a) physical similarity (eg, similar shape/name/colour), b) naming [eg, complete name not used, INN only used (acknowledging that some products sharing the same INN are approved for different uses]; • Clarity – Information may be unclear or misleading leading to inappropriate use; • Training – HCPs not trained in appropriate use <u>Types of Medication Errors</u> • Incorrect amount of product – Too little/too much – volume/dose/frequency • Use in an unapproved setting (eg, indication, patient population where no data to support use) • Incorrect route of administration / delivery device	*Not accepted.* *While such a grouping/classification might be useful if comprehensive and taking into account all possible causes and types of errors stemming from confusion of two medicinal products, a generic approach is preferred here.*
37	8.	Comment: Chapter 2 SCOPE Line 37 Please alter " vis a vis " as it has several meanings Proposed change : delete vis a vis and replace with "in relation to"	*Accepted.*
44	12.	Comment: Omission of 'upon'	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): “need to be carefully reflected *upon* and weighed against each other”	
49-53	9.	Comment: Please consider to change these lines for better readability. Also consider adding "new" to "Introduction of a new product….". Proposed change (if any): "Introduction of a new product that differs from an established product ~~as regards its concentration or strength, that is presented in a different pharmaceutical form, a new administration device or has a different composition or is intended to be used in a different patient population or indication,~~ in the following ways (including changes in concentration, strength, pharmaceutical form, device used, composition, patient population, indication, etc.), may in general…"	*Partly accepted.* *Wording changed.*
49-53	10.	Comment: Please consider to change these lines for better readability. Also consider adding "new" to "Introduction of a new product….". Proposed change (if any): "Introduction of a *new* product that differs from an established product ~~as regards its concentration or strength, that is presented in a different pharmaceutical form, a new administration device or has a different composition or is intended to be used in a different patient population or indication,~~*in the*	*Partly accepted.* *Wording changed.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		following ways (including changes in concentration, strength, pharmaceutical form, device used, composition, patient population, indication, etc.), may in general…"	
51	8.	Comment: 3.1, Potential Benefits. It should be noted that the indication and type of disease should be taken into account. Limited therapeutic alternatives or life threatening and chronic pathology are important considerations in justifying, for example extended release formulations that improve compliance Proposed change : Add " and the type of disease" after indication	*Not accepted.* *"New indication" covers "type of disease".*
54	12.	Comment: Specifically these products carry a potential risk for confusion with the reference product rather than simply "an inherent potential risk for incorrect use." Proposed change (if any): "On the other hand, such products may carry a potential risk for confusion with the reference product, leading to medication errors."	*Accepted.*
57	12.	Comment: Omit phrase 'it has to be kept in mind that' Proposed change (if any): "Drug therapy is generally…"	*Not accepted.* *Not deemed necessary.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
57	5.	Comment: The is ample evidence from patient safety reporting schemes that health care professionals make frequent errors when prescribing, dispensing, preparing, administering and monitoring medicines. Errors occur due to violations (when standardised working procedures are routinely ignored) or mistakes (knowledge based errors) or slips and lapses (involuntary mistakes). Proposed change (if any): Suggest delete paragraph completely as content indicates an incomplete understanding of basic patient safety theory.	*Not accepted.* *Mistakes in drug prescription/preparation/administration will inevitably happen. The focus lies on (potential) medication errors caused by confusion of two medicinal products. We still believe that the involvement of HC professionals can help mitigate the risk of medication errors.*
57	7.	Comment: "Well-trained staff" may not be aware of the changes with the new product that may lead to further medication errors. Proposed change (if any): No change as this is addressed further in the document	*Accepted.* *No action taken.*
57-60	9.	Comment: "It has to be kept in mind that drug therapy is generally prescribed and administered by well-trained experienced personnel, based on expert decision for treatment and – if drug not intended for self-administration - usually administered according to standardised working procedures. This will help reduce the risk of medication errors, but cannot always prevent them"	*Partly accepted.* *No action taken as some of the provided examples for medication errors (i.e. miscommunication, poor handwriting) lie beyond the scope of this paper. Others (i.e. packaging, naming, etc.) is already addressed in the paper.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		This section may be misleading as there are instances of health care professional medication errors and we should be sensitive to their needs. Proposed additional text: Medication errors occur for a variety of reasons, including those in the hands of healthcare professionals. For example, miscommunication of drug orders can involve poor handwriting, confusion between drugs with similar names, poor packaging design, and confusion of metric or other dosing units.	
57-60	12.	Comment: This paragraph seems to express the idea that medication errors related to product reformulations are less likely to occur if health professionals are prescribing and/or administering the products. Standardised working procedures may indeed mitigate the risk of errors, by ensuring that forcing functions, etc. are built into systems. However products that are not packaged/named or labelled for optimal safe use under real world conditions are still likely to be misused regardless of the level of expertise of the health professional responsible for administering the product. This paragraph seems to undermine the need for manufacturers to ensure adequate responsibility for the potential for medication errors. Proposed change (if any): This paragraph needs to emphasize the importance of patient safety issues in the naming/packaging/labelling of products in product	*Not accepted.* *The importance of naming/packaging/labelling issues has been addressed throughout the paper.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		reformulations.	
61	12.	Comment: The term “benefit-risk ratio” implies a specific, *quantitative* assessment of the relationship of benefit to risk. Proposed change (if any): Suggest ‘benefit-risk balance’ or ‘benefit-risk relationship.’	*Accepted.*
61-100	9.	Comment: Any place where the term "benefit-risk ratio" is used should be changed. Ratio implies a mathematical quantity which is not what is meant in this case Proposed change (if any): benefit-risk profile	*Accepted.* *Please see previous comment.*
64-65	2.	Comment: Excipients are the additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients. The growth of novel forms of drug delivery has resulted in an increase in the number of excipients now being used. Interest in the physical effects and properties of the excipients used in pharmaceutical formulations has increased in recent years as pharmaceutical scientists have become increasingly aware of the fundamental effects that excipients can exert on bioavailability, bioequivalence, and stability of formulation; excipients can no longer	*Not accepted.* *It is not agreed that certain excipients cannot be avoided or reduced.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		be regarded simply as inert or inactive substances. Relatively small variations in the physical properties of an excipient can produce significant differences in the behaviour of formulated products. Also may be worth noting that excipients are also used in other non-medicinal products e.g. confectionery, food products, cosmetics. Excipients can therefore normally not be avoided or reduced. Proposed change (if any): Please amend accordingly.	
66-68	12.	Comment: If a new product improves stability relative to the reference product why then should both products be kept on the market? Improved stability may reduce the likelihood of loss of efficacy and thereby reduce the risk of exposing patients to sub-therapeutic plasma concentrations. Proposed change (if any):	*Not accepted.* *Whether or not an "inferior" product will remain on the market is an issue that clearly exceeds the scope of the paper.*
69	5.	Comment: The benefits of providing new medicine products with a different concentration or formulation that facilitates safer practice are very important. We would like to highlight our support for this statement. Proposed change (if any):Leave unchanged	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
69	12.	Comment: "necessary dilution" should be replaced by "unnecessary dilution" which makes more sense in the sentence. Proposed change (if any): "…avoid unnecessary dilution…"	*Partly accepted.* *Added "otherwise" before "necessary".*
72-76	12.	Comment: Rephrase in order to improve the clarity of expression. Proposed change (if any): "This may reduce manipulation steps and thereby reduce the potential for errors in preparation. A more appropriate concentration/strength could also provide dosing flexibility…"	*Partly accepted.* *Slightly amended the sentence to move focus away from "safety of pharmacist/HC professional".*
74-76	7.	Comment: Different strengths may also support dosing adjustments for paediatric, elderly or those with metabolism deficiencies (hepatic, renal impairment etc) Proposed change (if any):	*Accepted.* *No action taken.*
75	10.	Comment: Benefits may include: decrease dose, concentration of Antigen (for vaccines), therapeutic protein, MAb etc.	*Accepted.* *No action taken.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
77-80	12.	Comment: Previous bullets are written in complete sentences. For consistency, need to use the same grammatical structure. Improve punctuation. Specify how liposomal formulations improve the benefit-risk balance. Proposed change (if any): Different formulations may offer advantages to patients, eg. : liposomal or other formulations that increase a product's efficacy while minimizing side effects; extended release formulations that improve compliance and may result in more consistent plasma concentrations; or formulations that are easier to administer for patients with dysphagia.	*Partly accepted.* *Grammatical structure amended, wording left unchanged.*
81	12.	Comment: For consistency, use complete sentences as per above. Proposed change (if any): "Some types or sizes of primary packages or administration devices may facilitate preparation and/or administration. Examples include patient-friendly packaging,…"	*Accepted.*
81	10.	Comment: Packaging instructions, types and sizes may also decrease medication errors.	*Accepted.* *No action taken.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
85	12.	Comment: For consistency, use complete sentences as per above. Proposed change (if any): "… not covered by the reference products, may be added to the MA.	*Accepted.*
91	5.	Comment: More information is required concerning potential new risks of new products of this type. In particular where an established proprietary name of s single product or range of products is routinely associated by healthcare professionals with a generic medicine and a new product is proposed that has the same proprietary name but different generic active. This will lead to confusion and errors by healthcare professionals and patients and there would need to be a very strong clinical rational for extending the product range in this way. Other potential risks include when the dose for a new formulation of a medicine differs significantly differs from the original medicine – overdose or underdose risk, or where there is a significant difference in the method the medicine is prepared, administered or clinically monitored. Proposed change (if any): Recommend a new section between 3.1 Potential benefits 3.3 Benefit/risk discussion	*Not accepted.* *Prescription and therefore use according to proprietary or generic names differs between member states. This issue is considered beyond the scope of this paper.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
92	12.	Comment: Improve the clarity of this paragraph by removing the initial phrase and rewriting the first sentence. Proposed change (if any): Paragraph to begin: "The potential advantages of reformulations need to be balanced against the additional risks and effects…"	*Partly accepted.* *Reworded first sentence for improved clarity.*
96	12.	Comment: What is meant by "the measures taken to avoid medication errors?" This needs to be clarified. Proposed change (if any):	*Partly accepted.* *Changed "the measures" to "any measures" to make clear. Very generally refers to whichever measures taken to avoid errors.*
96ff	1.	Comments: In line 96ff it is asked that justification should be provided in Module 3.2.P.2 "Pharmaceutical Development". The general aspects for the motivation of developing a particular dosage form/strength or formulation are usually contained in this part of the documentation. However, the potential risk deriving from the future presentation especially compared to already existing products in the market from other competitors are not known. The personal responsible for the pharmaceutical development have usually no	*Not accepted.* *The current situation is acknowledged. Stimulating an integrated approach to proactively tackling the issues raised would be an important future goal of this paper, though.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		access to this information and are not involved in the development of artwork/layout of packaging. Furthermore, the focus on pharmaceutical development is to improve the medicinal product regarding the effectiveness or to minimise the adverse drug reactions in order to support the patients' health. Usually, it cannot foresee in advance which medication errors might occur in future. Providing a justification in the Part 3.2.P.2 regarding medication errors is therefore hardly to realise in this dossier part. The same applies for clinical assessors: a benefit/risk discussion on the particular product compared with already existing products regarding efficacy is usually part of the clinical data. However, the presentation in the meaning of layout is not subject to this assessment. This is very difficult because the presentation of existing product may differ from country to country (in case of national, DCP and MRP-products) Proposed change (if any):	
96-98	9.	Comment: "Justification should be provided in the Pharmaceutical Development (3.2.P.2) of the application file as well as in other sections where appropriate (e.g. clinical data, benefit/risk discussion, RMP, etc.)." Please provide additional clarification regarding the	*Not accepted.* *This position paper is not a guidance document and must not be interpreted as such.* *Please also see the previous comment.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		expectation for the integration of information in Pharmaceutical Development (3.2.P.2) and clinical data, benefit/risk discussion, RMP to minimize medication errors. While pharmaceutical development information supports the selection of formulation and strengths which are evaluated in clinical trials, this section has not traditionally been focused on benefit/risk and Risk Management Plans and it is assumed that the relevance of 3.2.P.2 is restricted to physical attributes that are relevant to controlling medication errors. Proposed change (if any): If there is an expectation of this type of information to be included in Pharmaceutical Development (3.2.P.2), additional guidance would be required to supplement the current ICH CTD guidance.	
99	10.	Comment: If this is in the RMP, why add here? Redundancy should be avoided. We suggest EMA to propose avoidance of redundancy. Proposed change (if any):	Not accepted. *The issues presented in this paper might require to be addressed in different parts of a dossier. We do not agree that this ought to be seen as redundancy.*
100	12.	Comment: See line 61. Proposed change (if any): Suggest 'benefit-risk balance' or 'benefit-risk relationship.'	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
102	1.	Comments: At the time of application for marketing authorisation or variation a detailed discussion on potential incidence and/or severity of adverse events due to medication errors is hardly possible. Proposed change (if any):	*Partly accepted.* *It is agreed that it might be very difficult if not impossible to foresee the incidence of medication errors. One must not forget that this is about the anticipation of possible risks. However, with regards to severity of AEs caused by such errors, a meaningful scientific discussion is considered possible, taking into account (the AE profile of) products that the new one could be confused with.* *No action taken.*
102	5.	Comment: Medication error may not only involve dosing errors. Suggest following rewording: Detailed discussion required on the clinical requirements not being met or the incidence and severity of adverse events and/or medication errors associated with current medical products and how the introduction of the proposed new medical product could help minimise these risks.	*Partly accepted.* *Deleted "due to incorrect dosing".*
102-105 112-117	12.	Comment: These two paragraphs are repetitive and express similar ideas. They should be amalgamated. Interactions need to be considered when a reformulation with multiple ingredients is incorrectly administered in place of a reference product.	*Accepted*. *Bullet points 1 and 3 have been combined.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
104	1.	Comments: The applicant has not always access to all studies using dosage regimes different to those recommended in the SPC. We agree that products with known narrow therapeutic index should be assessed very thoroughly. Proposed change (if any):	*Accepted.* *No action taken.*
102-104	7.	Comment: in clinical trial settings it is unlikely that those enrolled will have loss of efficacy due to incorrect dosing. Such controlled settings are often criticised for not representing real-life scenarios due to relatively high adherence to prescribed medicines. Proposed change (if any): Such suggestions from clinical trials are not workable and need an alternative solution. One could be to include comment from non-biased key opinion leaders/recognised experts.	*Not accepted.* *The respective paragraph might have been misinterpreted. The possibility (incidence/severity) of medication errors ought to be discussed. Data from other trials/dosing regimens might inform such a discussion.*
107	7.	Comment: Although we agree with the suggestion there is no definition of a “narrow therapeutic index drug”? Unless defined this statement will not be	*Not accepted.* *Defining “narrow therapeutic index” is beyond the scope of*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		adhered to. Proposed change (if any): Include a definition of a "narrow therapeutic index drug"?	*the paper. Case-by-case judgment is considered necessary, as stated in the text.*
110-111	7.	Comment: Agree, but not limited to these examples. Proposed change (if any): Could include drug-drug interactions, those with metabolic deficiencies (eg hepatic, renal impairment etc)	*Not accepted.* *The list is intended to provide examples, not be comprehensive in covering all possible situations.*
110	1.	Comments: Information regarding the use in specific patient population (paediatric population, pregnant or breastfeeding women, elderly, etc.) are generally required and contained in the PIL/SmPC for all products. We agree that potential medication errors should be assessed under consideration of the circumstances of use (Rx/OTC; narrow therapeutic index; emergency use; special population group, etc.). On the other hand, all products are authorised by the responsible authorities, which approve the proposed product information SPC, PIL and labelling. The measure to highlight special information in SPC, PIL and labelling is however questioned. The strength and administered form is always part of the product name. This information is therefore present on every packaging component in dominant position.	*Accepted.* *No action taken.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The name of the medicinal product is mostly agreed prior the approval. Proposed change (if any):	
118-119	7.	Comment: Agree and feel that the importance of this is not stressed enough. Pack design is a key component and the need for industry consistency in packaging and description of the constituent (base not salt) and how the strength is displayed Proposed change (if any): To consider moving this higher up the paper and stressing the importance more.	*Not accepted.* *With regards to B/R assessment in light of potential medication errors, packaging etc. is one of several aspects to be considered. The list being referred to does not focus on recommendations for the Applicant.*
118-119	12.	Comment: Previous bullets are written in complete sentences. For consistency, need to use the same grammatical structure. Can consider including a broader list of examples of changes that help to differentiate reformulations from reference products. Proposed change (if any): "The applicant's proposals in the Risk Management Plan to clearly differentiate between the product…warnings on vials, etc. must be evaluated."	*Partly accepted.* *Wording amended as proposed.*
120	12.	Comment: It is clear that the risk of medication errors cannot be quantified. However, the risk can be characterized using software applications,	*Not accepted.* *This is a list of caveats and is not intended to make*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		visual/linguistic testing and expert evaluation. This paragraph seems to minimize the importance of ensuring adequate measures are taken to evaluate and reduce the risk of medication errors. Proposed change (if any): Remove this statement. Discuss the importance of advancing patient safety in the real world use of medications. There is a need to consider the circumstances or context under which the product will be used, and then to assess the implications of these processes on the risk of error.	*recommendations on how to address them.*
120	5.	Comment: We disagree with the statement in line 120,121 and believe that the level of risk and evidence of harm from sources such as the UK National Reporting and Learning System, signals a clear need for investment in development of a robust proactive approach to risk assessment. We suggest that with the involvement of appropriate stakeholder expertise, it is possible to develop a risk assessment tool and predictive indicators of the potential for harm Proposed change (if any): With appropriate user and manufacturer stakeholder involvement it should be possible to develop tools which allow predictive assessment of potential risks. The assessment should be used to inform advice on risk mitigation in the clinical setting.	*Not accepted.* *As of now, to our knowledge there is no tool that allows for quantification of the risk for confusion of medicinal products / medication errors caused and subsequent AEs accordingly. While the development of the necessary methodology would undoubtedly be helpful in addressing this issue in the future, the current setting is reflected on in the Position Paper.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
121	10.	Comment: "clinical use **cannot be accurately quantified** a priori." It is not clear why the risk of medication error cannot be reasonably determined based on differences in product profiles between established and new products. Proposed change (if any):	*Not accepted.* *While differences in product (safety) profiles can be determined, the same does not apply for the risk of medication error (due to confusion). Please see previous comment.*
122	9.	Comment: Not all following examples increase the risk of error, as stated, but they do impact it. Proposed Change (if any):' Nevertheless, certain circumstances that may potentially ~~increase~~ impact the probability of medication error warrant consideration, such as:'	*Accepted.*
123	5.	Comment: The list of bullet points that begins at line 123 could easily be developed as an exemplar checklist. Additional issues to be considered in a checklist Different active – same proprietary name? Different legal category? Different clinical indication? Different clinical contra-inducation Different dosage or frequency? Different formulation/excipient? Risk of look-alike name confusion? Different route of administration? Different clinical monitoring? Risk of look-alike label/pack confusion?	*Not accepted.* *The list is rather intended to provide examples, not be comprehensive or serve as a checklist.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Barcode and automation issues? Different concentration? Different pack size or quantity? Different storage requirements? Different length of expiry? Different drug – drug or drug device compatibility? Different method of preparation? Different method of administration? Different method of waste disposal? Electronic system issues?	
123-124	12.	Comment: It may be more relevant to mention products that are self-selected by a patient rather than self-administered. Proposed change (if any):	*Not accepted.* *Administration can be considered an additional "control step" where preceding confusion might become evident for a HC professional, but not for the patient.*
125	12.	Comment: The term 'correctly' is redundant. Proposed change (if any): " some kind of special training in administering…"	*Accepted.*
125-126	7.	Comment: This is unlikely to be successful. Who would do this? Pharmacy staff? Hospital teams? In current financial climate this is unlikely to work unless the new product price includes training resource needed. Proposed change (if any):	*Partly accepted.* *No action taken. Feasibility/scope of such training will not be discussed in the Position paper.*
129-130	12.	Comment: The use of the product in children does not increase the probability of error. Children as a vulnerable population is captured previously in line	*Not accepted.* *This does not refer to children being a vulnerable population*

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		111. Proposed change (if any): Omit this sentence	*but to the fact that dosing errors might more easily occur.*
131-134	12.	Comment: Consider using previously defined terms for clarity of language. Indicate the section in the paper where the "specific rules" can be found, eg. As outlined in section 4, or define these specific rules. Proposed change (if any): " The introduction into the market of reformulations may result in an increased risk of medication errors. Therefore, the applicant must justify that the benefits outweigh the potential risks linked with the introduction of the new product. In addition, specific rules as outlined in section 4 should be applied to reduce the risk."	*Accepted.* *Reference to section 4 inserted. Wording has been amended.*
131-134	7.	Comment: There should be "significant" benefit of the new product demonstrated in published head to head clinical trials. Otherwise such introduction will be simply considered as a means for pharmaceutical companies to increase profitability and also increasing confusion. Proposed change (if any): Include a statement that there should be significant benefits of the new product	*Not accepted.* *Discussing the motives for the development of new drugs is beyond the scope of this paper. Furthermore "Significant benefit" has a specific connotation in drugs regulation. No action taken.*
134	9.	Comment: This seems to suggest that any time a new	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		product that contains the same active substance(s) as an already-marketed product is introduced to market, "specific rules should be applied to reduce the risk." The application of interventions to minimize risks should be proportionate to the severity and the nature of the risks themselves. While an evaluation of the risk(s) of medication error(s) seems reasonable for all such new product applications, it is conceivable that when said evaluation has been performed, many such new products will not present a clinically important risk to patients (for example, if the change to the product involves re-formulation to eliminate a potentially toxic excipient). In this scenario, it should not be required to apply a specific intervention to reduce the risk. Proposed change (if any): Therefore, the applicant needs to undertake an evaluation of potential risks and has to justify that the benefits outweigh the potential risks linked with this new product. ~~In addition, when the benefit is well know, specific rules should be applied to reduce the risk~~ Appropriate and proportionate risk minimisation strategies should be proposed to reduce the risks when required.	
134	10.	Comment: This seems to suggest that any time a new product that contains the same active substance(s) as an already-marketed product is introduced to market,	*Accepted*.

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		"specific rules should be applied to reduce the risk." The application of interventions to minimize risks should be proportionate to the severity and the nature of the risks themselves. While an evaluation of the risk(s) of medication error(s) seems reasonable for all such new product applications, it is conceivable that when said evaluation has been performed, many such new products will not present a clinically important risk to patients (for example, if the change to the product involves re-formulation to eliminate a potentially toxic excipient). In this scenario, it should not be required to apply a specific intervention to reduce the risk. Proposed change (if any): It would be helpful to clarify what the expectations of pharmaceutical companies can be regarding "specific rules … to reduce the risk."	*Please see previous comment.*
134-171 (Section 4)	10.	Concur conceptually that educating pharmacists is a potentially meaningful way to reduce the risk of medication errors. However our experience with HCP education in Europe indicates that companies have limited access to non-physician health professionals for this type of intervention. We have been informed by our colleagues in Europe that in many EU Member States, nurses and pharmacists are off-limits for direct contacts from pharmaceutical companies. This is likely to present important limitations to the ability of	*Not accepted.* *Not in all cases specific measures are required. Therefore,*

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		companies routinely to propose pharmacist education as part of an EU RMP. Further, there is a request for evaluation of the effectiveness of routine risk minimization (labeling). While evaluations of the effectiveness of routine risk minimization are also mentioned in the final GVP V Guideline (Risk Management Systems), the conduct of such evaluations is requested to be performed "as applicable." It is not clear why the risk of medication errors in this special circumstance (a new product containing the same active substance as an old product) would in all cases require companies to perform a specific evaluation of the effectiveness of the prescribing information. Proposed change (if any):	*evaluation of their effectiveness is not relevant in all cases.*
138	12.	Comment: Improve readability. Proposed change (if any): Remove the phrase “are those which go beyond this and.” Sentence should read “Additional risk minimisation activities may include…”	*Accepted.*
138-140	7.	Comment: Healthcare staff are already bombarded with paraphernalia from pharmaceutical companies. If	*Partly accepted.*

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		the staff member choses to (for example) not read the letter from the company how will the risks be minimised. Such staff may also not have exposure to representatives. Proposed change (if any): There needs to be some consideration for those staff unable or unwilling to engage with communication from the pharmaceutical industry	*No action taken.* *This is acknowledged. However, the interaction between pharmaceutical industry and health care professionals is beyond the scope of the Position Paper.*
139	8.	Comment: 4. Risk Minimisation and Monitoring Education materials should not be restricted to physician, pharmacist or patient. It should concern all health care professionals such as nurses. Proposed change : Add “other healthcare professionals “ after pharmacist	*Accepted.*
140	10.	Comment: Agree with this paragraph, and in particular with the point that primary packaging needs to be clearly differentiating, so that even if the SPC isn't consulted, it will be clear to the healthcare provider which product is being used, and highlighting differentiating characteristics. Proposed change (if any):	*Accepted.*
142	12.	Comment: Specify section – 3.1	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
144-148	12.	Comment: This paragraph describes key risk minimisation measures and should be more fully developed. What are the guidelines or expectations with regards to labelling, packaging and naming of reformulations? As a minimum, it should be stated that packaging, labelling and naming should be selected so as to clearly distinguish the new product from the reference. Proposed change (if any): The introduction of new concentrations/strengths, formulations, dosage forms, preparations, excipients and target populations should be highlighted very clearly in SPC, PIL and labelling. As an important risk minimisation measure, the name of the medicinal product must be selected so as to be clearly distinguished from the reference product. The size and design of the container and/or packaging should also be considered.	*Partly accepted.* *Most ideas already reflected in original draft. Added "to avoid confusion" after "risk minimisation measure".*
144-149	2.	Comment: This bullet point specifically says risk minimisation measures include the NAME of the product and it seems to require approval. We consider that this has the potential to lead to nearly all packs being reviewed for names and packaging design under the risk	*Accepted.* *No further action taken.*

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		minimisation measures suggested if there is a new target population e.g. children's OTC cough and cold products. This will probably be picked up and included in the updating of the invented names guideline that is due for review soon.	
144-149	9.	Comment: An applicant must determine well before submission whether a new indication or dosage form will be a line extension (i.e. under the same MA) or a new MAA with a different name. The consequence of this is that the suggestion on lines 148/9 that the new (invented) names should be agreed prior to approval, i.e. during the dossier review process, is not practical for consideration of whether a product should have the same, a different, or a modification of the existing product's name.	*Not accepted.* *Not agreed. The judgment about the name will be made (also) on grounds of the possibility for confusion with existing names. The prior naming decision ought to take that into account, especially for new products.*
150	12.	Comment: User testing is a vital component to optimize safe use under real world conditions. User testing can be applied to packaging, labelling and product names. Proposed change (if any):	*Accepted*. *No action taken.*
150-151	10.	Comment: Please clarify timing. It is not clear whether the results of user testing have to be in CTD/RMP with filing or whether they should be submitted later.	*Accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
150 - 158	1.	Comments: Comment: A user testing is of limited value concerning the minimization of medication errors in special population groups like elderlies: In a study by the FDA that evaluated reports of fatal medication errors from 1993 to 1998, almost half of the fatal medication errors occurred in people over the age of 60. Older people may be at greatest risk for medication errors because they often take multiple prescription medications and they often not read and/or understand information's in PIL and labelling. Under these circumstances the important minimization strategy should be the duty to inform patients and consultation of physicians and pharmacists. It is not sufficient as proposed the "training of pharmacists and healthcare professionals" (line 152), rather the implementation and professional consultation of patients, especially the elderlies, are of essential impact. Training for healthcare professionals based on educational material is already required by health authorities for new products. It is not appropriate to require such material for all	*Partly accepted.* *The importance of medication errors in elderly patients is acknowledged, as is the fact that several of the topics touched upon on this Paper have been subject to other EMA guidance documents. Again, the focus of the present paper has to be kept in mind, as it mainly intends to raise awareness about the risk of confusion of two medicinal products and subsequent medication errors and possible strategies to address this issue during B/R assessment.* *In specific cases, a potential risk can be anticipated and proactive measures can be taken. This is the central subject of this paper.*

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		products. In case risks on medication errors became known authorities and MAH should agree mutually, which measure would be appropriate on a case-by-case basis. Thus, the first step should be the obligation to o monitor potential medication errors and to o include the results of this monitoring in the PSUR Health professionals, who give patients a prescription, should tell the name of the drug, the correct dosage, and what the drug is used for. Health professional should be sure that patient understands the directions for any medications patient may be taking including the correct dosage, storage requirements, and any special instructions. Apart from the comments on the suggested risk minimization strategies mentioned above, according to the guideline on the readability of the labeling and package leaflet of medicinal products from human use of European Commission, the user testing (line 150) is already implemented as part of CTD Module 1.3.4 of the application dossier (a user testing is always required for new applications; however, the user test refers to a particular PIL and is not performed under consideration of other existing products or	*The text has been slightly amended to clarify that user testing is intended for health care professionals as well, thus enabling the assessment of possible confusion with authorised/established products.* *(Please also see the following comment.)*

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		presentations, which may cause the risk for mistake). Also following suggestions for minimization of medication errors “very clearly highlighting in SPC, PIL, labelling in a name of a medicinal product, different vial sizes, design of packaging, etc” is already described in part in the mentioned above guideline with following wording “…Similarity in packaging which contributes to medication error can be reduced by the judicious use of colour on the pack…” Proposed change (if any):	
150-151	9.	Comment: At present, user testing is carried out on the package leaflet, and not on the instructions on how to handle the product, which are tested under ISO standards in the context of devices. Clarification should be given of the type of testing that may be needed, and the criteria that would trigger it. Also that bridging may be acceptable. Proposed changes (if any): A user test, which is able to prove that the instructions how to handle the product are clear and understandable (for example under ISO standards), should be performed and submitted before approval. A bridging report may be acceptable.	Partly accepted. *It is important to differentiate between obligatory user testing (of the PIL) and additionally useful user testing when there is an assumed risk of confusion to inform B/R as proposed here.* *Wording has been amended.*
152	7.	Comment: It is unlikely that staff will be released to attend training held by a third party in hospitals. The third party may not be permitted to do so either. This	*Not accepted.* *This is acknowledged. However, the interaction between*

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		suggestion may not be feasible in some organisations Proposed change (if any): To consider the success of training if pharmaceutical companies/third party training company are not able to access staff or organisation to improve awareness of safety of new product.	*pharmaceutical industry and health care professionals is beyond the scope of the Position Paper.*
152	9.	Comment: We concur conceptually that educating pharmacists is a potentially meaningful way to reduce the risk of medication errors. However our experience with HCP education in Europe indicates that companies have limited access to non-physician health professionals for this type of intervention. We have been informed by our colleagues in Europe that in many EU Member States, nurses and pharmacists are off-limits for direct contacts from pharmaceutical companies. This is likely to present important limitations to the ability of companies routinely to propose pharmacist education as part of an EU RMP.	*Not accepted.* *Please see previous comment.*
152	10.	Comment: Training pharmacists/healthcare professionals, based on approved educational material, should be offered by the MAH. Proposed change (if any): Training pharmacists/healthcare professionals *and/or specific informative communications to pharmacists/healthcare*	*Accepted.*

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		professionals based on approved educational material, should be provided by the MAH.	
150-153	2.	Comment: User test should be submitted before approval is mentioned as well as 'approved' educational material – approved by whom? Conditions of MA are being specified leading to potentially ever increasing requirements for OTC RMPs. Concerning user testing it is assumed that this applies to the Patient Information Leaflet. Proposed change (if any): Reword line 150 as follows: "A user testing of the Patient Information Leaflet, which is able to prove that…"	*Not accepted.* *User testing should not exclusively focus on the PIL but also on e.g. name and labelling.* *Please see the comment (by stakeholder 9) on this issue on page 58 of this document!*
152-154	9.	Comment: "Training pharmacists/healthcare professionals, based on approved educational material, should be offered by the MAH, if there is no possibility to implement all information needed for safe use of the product within SPC, PIL and labelling." In most cases it is expected that it will be possible to minimise the risks of medication errors within the SPC, PIL and labelling, therefore it would be better to reword this sentence as follows:	*Not accepted.* *The original draft is considered to transport the same message.*

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		Proposed Change: If there is no possibility to implement all information needed for safe use of the product within SPC, PIL and labelling, then training or education of pharmacists/healthcare professionals, based on approved educational material, should be offered by the MAH.	
156-158	9.	Comment: Propose rewording for clarity. Proposed change (if any): The content and format of the educational material will need to be agreed with the National Competent Authority ~~prior to~~ upon by the conclusion of the applicable procedure and included in the final assessment report to enable its use at launch within each member state.	*Not accepted.* *Not considered necessary.*
156-158	10.	Comment: Propose rewording. Proposed change (if any): The content and format of the educational material will need to be agreed ~~with the National Competent Authority prior to~~ *upon by the conclusion of the applicable procedure and included in the final assessment report to enable its use at* launch within each member state.	*Not accepted.* *Not considered necessary.*
161	8.	Monitoring of effectiveness Surveys should be added Proposed change: Add “and surveys” after monitoring	*Not accepted.* *Not considered necessary.*
163	12.	Comment: Monitoring all medication errors – including	*Accepted.*

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		those that do not necessarily result in adverse reactions – is preferable. For example, near misses are a valuable source of information as to how a product is being used in clinical practice yet by definition do not result in ARs. All *potential* errors need to be included in the monitoring process. Proposed change (if any): Remove the phrase "resulting in adverse reactions."	
165	7.	Comment: PSUR is an acronym that may not be understood by all Proposed change (if any): Expand the acronym	*Accepted.*
165-168	2.	Comment: The MAH considers PSURs in themselves not to be the appropriate tool for monitoring the effectiveness of any risk minimisation activities. Monitoring of the effectiveness of risk minimisation measures should be detailed in the risk management plan as outlined in section V B 11.5 of module V. Increasing the number of PSURs to be written is not a risk minimisation activity in its own right and contravenes one of the key goals of the New Legislation to simplify pharmacovigilance processes. Moreover, providing a higher number of PSURs is not considered helpful in this instance. Instead, the MAH should have robust	*Not accepted.* *PSURs are considered one useful tool besides others to address the issue of medication errors.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		pharmacovigilance procedures in place to monitor the effectiveness of risk minimisation measures independent of the production of PSURs. Proposed change (if any): Please delete lines 165-168.	
165-168	11.	Comment: The MAH considers PSURs in themselves not to be the appropriate tool for monitoring the effectiveness of any risk minimisation activities. Monitoring of the effectiveness of risk minimisation measures should be detailed in the risk management plan as outlined in section V B 11.5 of module V. Increasing the number of PSURs to be written is not a risk minimisation activity in its own right and contravenes one of the key goals of the New Legislation to simplify PV processes. Also providing a higher number of PSURs is not considered helpful in this instance. Instead the MAH should have robust pharmacovigilance procedures in place to monitor the effectiveness of risk minimisation measures independent of the production of PSURs. Proposed change (if any): deletion of lines 165-168.	*Not accepted.* *Please see previous comment.*
165, 168	12.	Comment: Sentence structure needs to be consistent with other bullets.	*Partly accepted.*

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): (165) Suggest deleting "and/or commitment to submit." Replace with "submitting PSURs…" (168) "shortening of PSUR cycles in regard to monitoring a specific risk."	*Wording of last bullet point amended.*
168	9.	Comment: We believe that the benefit of monitoring of the effectiveness of risk minimisation measures by shortening the PSUR cycles is questionable. PSUR preparation covers many issues other than a specific potential/identified risk thus not contributing directly to an increased awareness of the effectiveness of the risk minimisation measures. Proposed change (if any): We suggest that in alternative to the shortening of PSUR cycles, special evaluations on the specific risk effectiveness could be provided by marketing authorization holders.	*Not accepted.* *Please see comments on page 62 and 63 of this document regarding the suitability of PSUR as a vehicle to address medication errors.*
169-171	2.	Comment: "The effectiveness of all the risk minimisation measures (change of name, product information, educational material, user testing) in place should be re-evaluated in accordance with defined time-intervals…". How does one measure this effectiveness? Is there an	*Not accepted.* *Beyond the scope of the paper.* *This is not a guidance document and must not be read as such.*

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		agreed model to follow? It continues on to say very clear and prominent labelling in the product information and packaging have to be implemented. Add 'where appropriate'? There will be a lot of subjectivity with this type of assessment for OTCs which ideally should have lower potential for errors because of the use of pack designs compared to prescription products' livery. The potential situation might occur that, due to the development of educational materials to minimise medication error risks the effectiveness of which could be monitored e.g. within the RMP, a MS could decide to bring these educational materials to the PRAC attention and trigger that the new OTC product may be finally included in the public list of medicinal products subject to additional monitoring. Such a procedure can be triggered "when a marketing authorisation is granted subject to, e. g. taking certain measures for ensuring the safe use of the medicinal product to be included in the RMP." Proposed change (if any): It should be stated in the position paper that such measures shall not automatically trigger the inclusion of a non-prescription medicinal product in the optional scope of the list subject to additional monitoring.	

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173-175	12.	Comment: Clarify the language. It is not necessarily accurate to state that a new product will generate "an increase in risk of medication errors as compared with the original product." It is more specifically that a new product carries a potential for a risk of *confusion* with the original product, leading to medication errors. Proposed change (if any): "In developing new presentations of existing medicinal products, the potential for confusion with the original product should be considered."	*Partly accepted.* *Wording clarified.*
181-182	12.	Comment: Improve the grammatical structure. Proposed change (if any): "Following this principle, it is important that the applicant be able to justify such an application by demonstrating a prevailing benefit to counterbalance the potential product-associated, increased risk of medication error."	*Accepted.*
184	12.	Comment: Need to specify the timeline for implementing risk reducing measures. Proposed change (if any):	*Not accepted.* *Not deemed necessary.*