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Good practice guide on risk minimisation and prevention of medication errors

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Executive summary

Medication errors present a major public health burden and there is a need to optimise risk minimisation and prevention of medication errors through the existing regulatory framework. The European Medicines Agency (EMA) in collaboration with the EU regulatory network was mandated to develop regulatory guidance for medication errors, taking into account the recommendations of a stakeholder workshop held in London in 2013. This guidance is intended to support the implementation of the new legal provisions regarding the reporting, evaluation and prevention of medication errors and is intended mainly for the pharmaceutical industry and national competent authorities. Healthcare professionals (HCP) are expected to consult national clinical guidance on reducing the risk of medication errors.

This good practice guide is one of the key deliverables of the Agency's medication error initiative and offers guidance on risk minimisation and prevention of medication errors. The guidance includes population-specific aspects in paediatric and elderly patients, as well as guidance on the systematic assessment and prevention of the risk of medication errors throughout the product life-cycle.

The key recommendations:

- The potential for medication errors should be considered at all stages of the product life-cycle but particularly during product development.
- To minimise the risk of medication errors
 - careful consideration should be given to the name and pharmaceutical design of a medicinal product (including its type of dosage form, appearance and other formulation characteristics, packaging and labelling) in order to minimise the risk of mix-ups between different products;
 - the product information should inform HCPs, patients and caregivers of the most appropriate use of the product.
- Where medication errors result in adverse outcomes, corrective actions should be taken.

1. Introduction

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. This includes the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product. Examples of common medication errors include giving a medication to the wrong patient, the wrong dose of a medication being given to a patient or forgetting to give a patient a medication that had been prescribed for them. Competent authorities in EU Member States, marketing authorisation holders (MAHs) and the Agency have a number of obligations as detailed in Title IX of Directive 2001/83/EC, Regulation (EC) 726/2004, chapter 3, Article 28 and (for those medicinal products supplied with CE marked devices, Directive 93/42/EEC, Article 10 and Annex I). These relate to the recording, reporting and assessment of suspected adverse reactions (serious and non-serious) associated with an error in the prescribing, storing, dispensing, preparation or administration of a medicinal product for human use authorised in the European Union (EU), including scientific evaluation and risk minimisation and prevention.

Medication errors represent a significant public health burden, with an estimated global annual cost exceeding €4¹. Individual studies have reported inpatient medication error rates of 4.8% to 5.3% and

¹ http://www.who.int/patientsafety/information_centre/reports/Alliance_Forward_Programme_2008.pdf

in another study, prescribing errors for inpatients occurred 12.3 times per 1000 patient admissions². In most cases medication errors are preventable, provided that the potential risks of medication errors have been considered during the product development, appropriate measures put in place and reactive measures taken in response to documented reports of medication error. It is important that reports of medication errors and interventions are evaluated, and corrective and preventative actions considered, proportionate to the risk and in accordance with quality management systems, as described further in Good Vigilance Practices (GVP) Module I - Pharmacovigilance systems and their quality systems³.

This good practice guide is complementary to the guideline on GVP and the scientific guidelines on quality, safety and efficacy of medicines published on the Agency's website, including the position paper on potential medication errors in the context of benefit-risk balance and risk minimisation measures (EMA/CHMP/277591/2013)⁴.

2. Scope

This good practice guide outlines the key principles of risk management planning in relation to medication errors arising from the medicinal product and its delivery system (if applicable). This includes medication errors related to the name and the design of the product, with a special focus on the type of dosage form, the type of administration device (if applicable) and the packaging. This guidance describes the main sources and categories (types) of medication error which may need to be considered, provides real-life examples of such errors, the measures implemented to minimise the risk of medication errors occurring and suggests proactive approaches to risk management planning throughout the product life-cycle. This guidance should be read in conjunction with the latest version of GVP Module V on risk management systems and GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators. The recording, coding, reporting and assessment of medication errors is covered in a separate document (see section 5.1.1.)

Risk management planning in relation to events associated with intentional overdose, abuse, misuse, occupational exposure, off-label use and of medication errors occurring in the context of clinical trials conducted in accordance with Regulation (EU) No 536/2014, repealing Directive 2001/20/EC, are outside the scope of this guidance.

3. Legal basis

Directive 2001/83/EC specifies that the definition of the term 'adverse reaction' covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The risk management system (described in Directive 2001/83/EC) documents the risks which may be associated with use of a medicinal product, including those which arise from medication errors and any measures which may mitigate these risks. Commission Implementing Regulation 520/2012 defines the content and format of the risk management plan (RMP).

4. Definitions

The definitions provided in Article 1 of Directive 2001/83/EC and those provided in chapter 4 of the good practice guide on recording, coding, reporting and assessment of medication errors (see section

² Medication Errors: An Overview for Clinicians Wittich, Christopher M. et al. Mayo Clinic Proceedings , Volume 89 , Issue 8 , 1116 - 1125

³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf

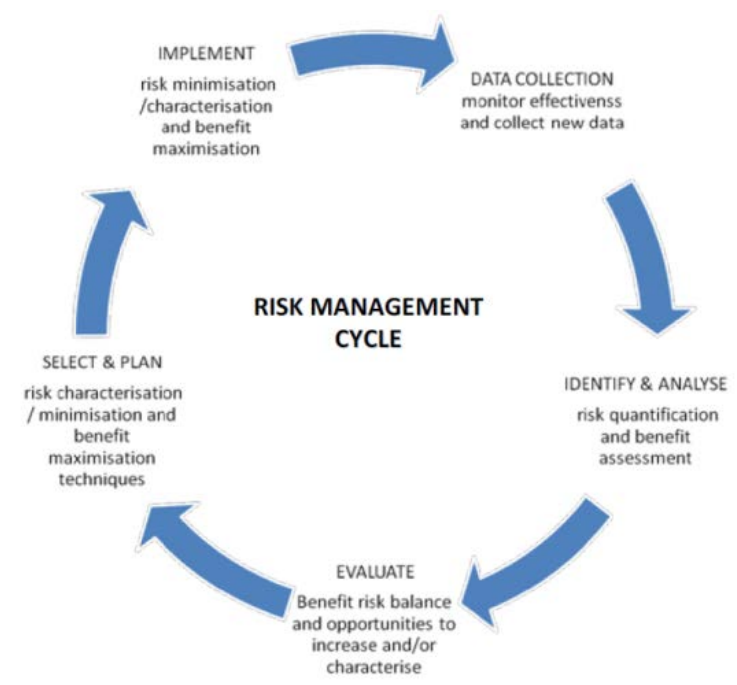
⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144096.pdf

5.1.1.) should be applied for the purpose of this guidance; of particular relevance for risk minimisation and prevention of medication errors are the definitions provided in GVP Module V on risk management systems (Rev 1) which include the general principles presented in the ICH-E2E guideline, and GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators (Rev 1).

5. Structure and processes

5.1. General principles of risk management planning and the tools used

GVP Module V describes the general principles of risk management planning, which is a global process, continuous throughout the life-cycle of the product. It involves the identification of risk at the pre-authorisation phase, during evaluation of the marketing authorisation application and post-authorisation phases. It also involves planning of pharmacovigilance activities to monitor and further characterise risks, planning and implementation of risk minimisation activities and measurement of the success of these activities.



Risk management planning in relation to medication errors should be proactive, beginning at an early stage in product development and continuing with the development of newly marketed products (which could be used with the concerned product) and with any changes to the use of the product in clinical practice. Medication errors can arise at any stage of the treatment process, including prescribing, storing, dispensing, preparation for administration or administration. Such errors can lead to over- or underdosing, incorrect application via the wrong route of administration or administration to the wrong patients. The consequences may include serious adverse reactions including death, an increased incidence and/or severity of adverse reactions and loss of effectiveness.

During the product development process, applicants should consider the various sources of medication error, their relevance for the product and the likely impact on the balance of risks and benefits. This should take into account relevant products in the same or similar indication(s) already on the market. Once the product is marketed, MAHs should consider whether any significant changes to the marketing

authorisation may increase the risk of medication error. Such changes may include (but are not limited to) the introduction of a medicinal product that differs from an authorised/established product regarding the

- product name,
- concentration or strength,
- pharmaceutical form,
- composition,
- method of preparing for administration,
- route of administration,
- administration device (or method of supply of administration device),
- patient population or indication,
- inbuilt distinguishing features in terms of appearance (e.g. appearance of insulin pen device).

The RMP may be used to document safety considerations given to the product design (as applicable) and should be kept updated during the product life-cycle. The RMP may provide detailed descriptions of medication errors in relation to the product design (including packaging), pharmaceutical properties and pharmacology of the product, and at all stages: dispensing; preparation for administration; and administration. The RMP may also include aggregated data in the form of a summary of medication errors identified during the clinical trial programme (and any corrective and preventative measures taken as a result of these reports), the effects of device failure (where a device component forms an integral part of the medicinal product as well as co-packed medical devices) and a summary of any medication errors reported with the marketed product. Any risk minimisation measures proposed by the MAH to reduce confusion between newly marketed and existing products (where significant changes to the marketing authorisation or line extensions have been introduced) should be discussed in the RMP.

Situations where medication errors may occur but where the impact of medication errors occurring is uncertain may represent a potential risk (e.g. risk of overdose resulting from inaccurate dosing of an oral liquid medication, risk of decreased efficacy resulting from difficulty using the administration device). Where reports of medication errors have been received which have resulted in adverse outcomes, medication error (specifying the adverse outcome) should be considered an identified risk. The decision whether to classify the adverse outcome due to a medication error as an important risk will depend on the number of cases reported in clinical trials or in post marketing use and also on the level of risk associated with this error. A medication error leading to a risk which impacts on the benefit-risk balance of the product or which has implications for public health may be considered an important safety concern and included in the RMP. Both routine and additional risk minimisation measures may be implemented to reduce the risk of medication errors.

Furthermore, MAHs have an obligation to describe and discuss patterns of medication errors and potential medication errors within every periodic safety update report (PSUR), even when these are not associated with adverse outcomes. Development safety update reports (DSURs) should also include any evidence of clinically significant medication errors. The context of product use should be considered and discussed in relation to these reports, including: the setting of use; stage of medication process; category (type) of medication error; contributing factor(s); medicinal product(s) involved; variables amongst the treated population; patient outcome(s); seriousness; region/country of occurrence; and mitigating factors. The context of reports of medication errors is relevant not only for root cause analysis (RCA) but also for developing appropriate risk minimisation measures.

5.1.1. Reporting and Coding of medication errors

Guidance on the reporting and coding of medication errors is provided in the good practice guide on recording, coding, reporting and assessment of medication errors (EMA/762563/2014).

5.1.2. Root cause analysis

Individual cases of medication error should be properly followed-up in the first instance, in order to obtain an accurate version of events and factors contributing to the adverse event as described in GVP Module VI⁵ and which is further described in the good practice guide referred to in section 5.1.1. A root cause analysis (RCA) may then be applied to analyse medication error situations or even specific events when determining what actions to take. A pharmaceutical quality system will likely already include RCA applied to investigations of deviations and suspected product defects, but the methodology may be of use in the investigation of medication errors. The goal is to identify both active errors (errors occurring at the point of the interface between humans and a complex system) and latent errors (the hidden problems within healthcare systems that contribute to the event). Any RCA undertaken should be proportionate to the consequences of the issue. The analysis should be approached broadly, considering the sequence of events that may have led to the error. MAHs and parties involved in the manufacture, research, sale or supply of the product should contribute to the analysis of events.

5.1.3. Use-related risk analysis and Human Factor/Usability Engineering

Risk management is an important part of the development of medicinal products with delivery systems. Risk management involves systematic application of policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

The US Food and Drug Administration (FDA) has issued guidance⁶ on safety considerations for product design to minimize medication errors; this guidance is complementary to EU guidance and is not binding in the EU, but may be useful to consider. The FDA guidance recommends two tools in particular, "failure mode and effects analysis" and "simulated use testing" (also known as "human factors" or "usability" or "user" testing). However, other risk management tools are available, including the "Fault-Tree-Analysis" and "Hazard Analysis", which may be equally effective in the management of risks. The report of the stakeholder workshop on medication errors⁷ in 2013 notes the pharmaceutical industry's suggestion to use other methods of human factor engineering to inspect the usability of the product, including cognitive walkthrough, heuristic evaluation and task analysis methods such as the "perception-cognition-action" (PCA) analysis, to be carried out early in development. Ultimately, the applicant should select the most appropriate risk management tools to investigate product usability.

For medicinal products delivered via an administration device, the relevant harmonised standards are EN 14971 Application of Risk Management to Medical Devices and ISO/IEC 62366: Medical Devices – Application of Usability Engineering to Medical Devices⁸. These are applicable throughout the administration device life-cycle (from development to decommissioning).

5.1.3.1. Failure mode and effects analysis

The Institute for Safe Medication Practices (ISMP) has issued guidance on the principles of conducting failure mode and effects analysis (FMEA)⁹. Broadly, this involves analysis of all the potential sources of

⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144009.pdf

⁶ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm331808.htm>

⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf

⁸ http://www.iso.org/iso/catalogue_detail.htm?csnumber=38594

⁹ <https://www.ismp.org/tools/FMEA.asp>

medication error before they occur, in the situations under which they may occur (e.g. prescribing, dispensing, preparation and administration). The FMEA proactively considers 1) the processes in each situation, 2) possible failures (what might happen), 3) the possible causes, 4) the effects on the patients, 5) the severity of the effect on the patient, 6) the probability the error may occur (which collectively suggest how much of a hazard is presented) and 7) proposed actions to reduce the occurrence of failures.

In addition to errors which may be due to product design (some examples of which are provided in Annex 1 of this guide), errors may relate to the product name, labelling and marking with Braille, packaging and issues relating to storage of medicines. For this reason, it is recommended to use the intended packaging and labelling as early as possible in the assessment of potential medication errors, to assist with early detection of potential problems.

5.1.3.2. Human factors testing

Human factors testing can explore whether instructions for use can be adequately understood and followed by users. Where simulated use testing has been performed, the results of this can be provided as supporting evidence in EU marketing authorisation applications. Such data may also be requested during the assessment of the application if assessors have concerns over the risk of medication errors. For a medicinal product delivered using a non-reusable, single unit integrated administration device, compliance with Annex I of the Medical Device Directive 93/42/EEC¹⁰ is required to assure the safety and performance of the device. A number of other EU harmonised standards^{11,12,13} can be applied where relevant, i.e. where the medical device is incorporated into or supplied with a medicinal product, to demonstrate compliance of use safety requirements of Annex I of the Medical Device Directive. For medicinal products not associated with an administration device, Annex I requirements do not apply.

5.2. Assessing the potential for medication errors during the product life-cycle

5.2.1. General considerations for potential sources of medication error

There are numerous potential sources of medication error and it is therefore important to fully consider and evaluate which errors may arise, at what stage they may occur, whether these are likely to have consequences in terms of safety outcomes or loss of efficacy and which measures may mitigate the risk of medication errors occurring. Although some medication errors may occur at the treatment phase, some may be identified at the product design stage, by considering the ways in which the products will be used and whether there is any potential for error¹⁴.

Product design

Many different dosage forms are available and all may be associated with medication errors, depending on the intended user and the setting of use. A number of common sources of medication errors are described in Annex 1 of this guide and include the appearance, size and shape of tablets, dilution problems with concentrated solutions and issues with the application and disposal of patches.

Applicants should proactively consider all aspects of the design of the product, how it will be used, in which environment it will be used, and who will use it and conduct a suitable analysis of the potential for medication errors (see section 5.2.3.). Further to this, applicants should consider which elements of

¹⁰ http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm

¹¹ EN ISO 14971:2012 - Risk Management

¹² EN ISO 13485:2012 – Quality Management System, specifically section 7.3.6 (Design and Development Validation)

¹³ IEC 62633:2015 – Application of Usability Engineering to Medication Devices

¹⁴ In the UK, the Department of Health has issued guidance on a system-wide design-led approach to tackling patient safety in the British National Health Service (<http://www-edc.eng.cam.ac.uk/medical/downloads/report.pdf>)

the design of the product may reduce the risk of medication errors; a number of suggestions are included in Annex 2.

For non-prescription products, additional consideration should be given to possible sources of medication errors when the product is used without the supervision of a HCP and what measures could be put in place to mitigate such errors.

Medication Errors in the context of the available range of therapies

It is important to explore the potential for medication errors in the context of the available therapies and the use of any newly marketed product among these. This requires an overview of available treatment options at the EU Member State level and consideration of whether there is the potential for confusion of mix-ups between products due to similarities in posology, appearance, method of administration, strength or packaging. Final mock-ups of the leaflets and labels for marketed medicines are not always made publicly available through the websites of national competent authorities or marketing authorisation holders. However, public health would be improved by making these materials publicly available as this would allow applicants to design labelling which differs sufficiently from other products to reduce the likelihood of mix-ups between products.

5.2.2. Typical errors during the clinical trial programme

Subjects in clinical trials are typically closely monitored and have contact with study investigators during the trial according to the frequency defined in the study protocol. This controlled environment may therefore not reflect real world use, but even in the clinical trial scenario, medication errors may still occur.

Common sources of medication errors in clinical trials may relate to use of small font sizes and absence of information on dose/strength in the plain packaging used for investigational products. The use of multi-language labelling often leads to the use of very small font size, with precautions and warnings for use included in a small label in a multi-language page. Additionally, medication errors can also occur in clinical trials due to the way investigational products are packaged. In one trial for example, trend analysis showed that there was an increasing number of overdose events. A RCA determined that this was related to poor packaging design, where patients were provided with multiple dose strengths in one secondary package (carton). A number of patients that were on the low dose of the drug were unnecessarily receiving large quantities of the higher doses, simply to make the drug supply easier. This resulted in confusion and overdose and the packaging was therefore amended.

Usability studies and clinical studies have different objectives and for this reason, inclusion of a usability study in a clinical trial setting is not usually recommended. Simulated use testing conducted with representative users under reasonably realistic conditions of use is generally sufficient to evaluate use-related risks. Simulated use studies allow for an early indicator of refinements that may need to be made to the design of the product or instructions for use prior to labelling, approval and marketing. However, in cases where the type of administration device or the use environment is complex and the conditions of use are not well understood, it might be necessary to validate a device under conditions of actual use. Actual use studies, if conducted, should be observed and assessed by a human factor expert.

During clinical trials, any clinical complaints or use-related adverse events which are considered unrelated to protocol deviations may be collected to further understand potential use-related errors. In this scenario, applicants should provide an appropriate risk analysis for medication errors detected in the clinical trial programme and use this as a basis for refinement in the proposed pharmacovigilance and risk minimisation activities (or both).

5.2.3. Defects and device failure (pre-authorisation)

Products which incorporate devices for administration where the device and the medicinal product form a single integral product designed to be used exclusively in the given combination and which are not reusable or refillable (e.g. a syringe marketed pre-filled with a drug) are covered by pharmaceutical legislation. However, in addition to this, the relevant essential requirements in Annex I of the Medical Devices Directive 93/42/EEC¹⁵ also apply with respect to safety and performance related features of the device (e.g. a syringe forming part of such a product). Compliance with harmonised standards under Medical Device Directive 93/42/EEC for medical devices is recommended.

Applicants should systematically assess risks throughout development taking into account all known information, which may include output from post-market experience with similar products, human factor engineering/usability engineering studies and clinical experience (e.g. clinical complaints).

Some of the medication errors related to medicines administered via devices are described in Annex 1 of this guide but these largely relate to errors which may occur even when the medicinal products are within quality standards or devices are functioning normally. The manufacturer should assess known and foreseeable hazards associated with the medical device in both normal (intended use) and fault conditions. It is also important to consider that medication errors may arise when a) medicinal products are defective, b) medical devices fail or are found to be defective (see examples below and in Annex 1) or c) patients or HCPs accidentally misuse the product. Further information on the distinction between a product quality issue and a medication error is included in the good practice guide referred to in section 5.1.1.

For medicinal products delivered via an administration device, applicants should consider the likelihood of common problems such as blocked or blunt needles, mix-ups between products presented in similar devices (e.g. low- and high-strength insulins), needles being of an appropriate length to deliver the medicinal product to the correct site of administration, or non-functioning of inhaler devices under normal conditions of use or after dropping of the device. Other examples are described in Annex 1 of this guide and in the addendum on a risk minimisation strategy for high-strength and fixed combination insulin products (EMA/686009/2014).

5.2.4. Medication errors resulting in harm during post-authorisation use

Although the risk of medication errors can be considered during the product design stage and using data gathered from the clinical development programme, it is not until real life use in the post-marketing environment that some medication errors will be identified. This may occur at various stages of the treatment process and involve multiple HCPs and other stakeholders.

The following information relates to medication errors which may be identified in post-marketing use and may frequently arise from the appearance of the product or its labelling.

Prescribing

A prescription is a written order, which includes detailed instructions of which medicinal product should be given to whom, in which formulation and dose, by which route, when, how frequently and for how long. Thus, a prescription error can be defined as a failure in the prescription writing process that results in a wrong instruction about one or more of the normal features of a prescription. Medicinal products are most commonly prescribed by physicians but can also be prescribed by other HCPs with appropriate training including nurses, dentists, pharmacists and optometrists. It is therefore important that MAHs note the errors that may be introduced at the prescription stage and ensure that product information provides information on the posology. This should make clear for each indication: the

¹⁵ http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm

correct dose, the strength of product to be used, the route of administration/pharmaceutical form, the length of treatment, the instructions for dose titration, the most appropriate dosing time (if this is important) and whether the medicines can or should be taken with food and drink.

Where medicinal products are self-administered by patients, the underlying reasons for medication error or accidental over- or underdose may include lack of understanding of the dose regime. There are also specific situations that should be considered by MAHs, which may be particularly associated with medication errors if errors in dosing occur, such as use of medicinal products with a narrow therapeutic window or which are toxic when overdosed.

It is important to consider situations when a product range includes both immediate-release and modified-release formulations. In this scenario, MAHs should ensure that there is differentiation in packaging and naming between these products and that the instructions for use by patients and carers emphasise that modified-release formulations should not be crushed or chewed as applicable.

Dispensing

Prescriptions are largely dispensed in both hospital and community pharmacies. Errors may be introduced by selection of the wrong product from the shelf, in terms of wrong drug, formulation, dose or strength. Such errors may arise due to similarities in packaging design, strength not being clearly highlighted and similarities in the (invented) name between products.

It is not mandatory for a generic product to have the same characteristics as the innovator (e.g. in terms of colour, size and shape of the tablet or capsule), however this may reduce the risk of medication errors at the dispensing stage. There is also some evidence that variation in the appearance of marketed or generic products can lead to patients discontinuing essential treatment early¹⁶.

Preparation and administration

Some medicinal products for intravenous (IV) use or parenteral administration require preparation, dilution or reconstitution prior to use and this may introduce medication errors. Treatments given by the IV route are associated with the highest rates of preparation and administration errors due to issues such as incompatibility with diluents or by injecting bolus doses faster than the recommended slower infusion time. Medicinal products for IV use may be inadvertently given by the subcutaneous (SC), intradermal or intra-muscular (IM) route rather than by infusion. A further source of error may be the use of medicinal products which have expired or been stored incorrectly (for example at the wrong temperature), which may lead to loss of efficacy; storage information is a standard piece of information included in the SmPC, package leaflet (PIL) and label. Related to this, for sterile products because it is difficult to predict all the possible conditions under which the product will be opened, diluted, reconstituted and stored, the user is responsible for maintaining the quality of the product that is administered to the patient. In order to help the user in this responsibility, the MAH should conduct appropriate studies and provide the relevant information (e.g. on the recommended storage temperature and shelf-life of the product after reconstitution) in the user information texts (e.g. SmPC, PIL and labelling). Further guidance on labelling is provided in the note for guidance on maximum shelf-life for sterile products for human use after first opening or following reconstitution (CPMP/QWP/159/96 Corr)¹⁷.

The use of multiple dose units to achieve a single dose (i.e. multiple vials of a drug or combinations of different tablet strengths) may be problematic if the number of dose units used is not closely

¹⁶ Aaron S. Kesselheim, Katsiaryna Bykov, Jerry Avorn, Angela Tong, Michael Doherty, Niteesh K. Choudhry. Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction. *Annals of Internal Medicine*, 2014; 161(2):96

¹⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003476.pdf

monitored and not recorded during administration. Patients may also not receive medication at the right time (e.g. on an empty stomach or in the morning rather than in the evening). Many of these problems may arise if there is any ambiguity over the information presented in product information. Well-designed leaflets for patients and labelling of the product can ensure that key information on optimum administration of the product is featured prominently.

There is also the potential for errors in administration by visiting HCP and carers, who may be carrying multiple individual products for different patients in the same bag. Here, clear identifying features of a product can help to distinguish between products (e.g. ensuring that the presentation of a product, such as an insulin pen, differs to others of the same class so that they are less easily mixed up). Specific risk minimisation strategies e.g. for high strength and fixed combination insulin products administered in pre-filled pens is provided in the addendum to this good practice guide.

Device-related medication errors

A number of other examples of device-related medication errors are included in Annex 1. Where such device-related medication errors are reported, MAHs should follow up reports to obtain additional information as necessary and investigate whether the reports are substantiated, are isolated examples or are batch-wide and batch-specific. Further guidance on the elements of medication errors relating to defective medicines which should be reported or followed up for further details are included in the good practice guide referred to in section 5.1.1.

6. Risk minimisation

6.1. Risk minimisation measures

Risk minimisation activities can mitigate the risk of medication errors related to the medicinal product.

This guidance is complementary to the recommendations in GVP Modules V and XVI which offer guidance on the concepts of risk minimisation tools and their development.

Examples of routine risk minimisation

Where a product is administered by injection or IV infusion, the product information should explain the different approaches to preparation and administration as applicable and make clear if an injected product should not be given by a specific route (for example IV, SC or IM).

Pack size limitations can reduce the risk of medication errors in situations where there have been reports of patients taking too many tablets (leading to overdose). Limiting the pack size requires the patient to return to the prescriber when more medication is required, which gives the prescriber an opportunity to check the status and progress of the patient and that the medicine is being used correctly.

It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and PIL may be overlooked by HCPs, patients or care givers. In line with Article 54 of Directive 2001/83/EC specifying the particulars that should appear on the outer and immediate packaging there is provision in the Quality Review of Documents (QRD) template to include key information on the administration of the product, for example in section 5 'method and route of administration' or in section 7 'other special warning(s) on the outer packaging, if necessary'. Such warnings should be reserved for situations where they are considered very important in order to fulfil a risk minimisation objective (for example warnings were included in section 7 for Toujeo to avoid any overdose: "Use only in this pen or severe overdose can result. Always use a new needle for each injection").

In rare situations, it may be necessary for some products to include additional warnings in labelling which are not required for other products (e.g. the labels for generic piperacillin/tazobactam carry a statement that it must not be mixed or co-administered with any aminoglycoside, and must not be reconstituted or diluted with lactated Ringer's (Hartmann's) solution; a similar warning is not required for the originator product which has been reformulated to remove these incompatibilities).

Although all product information includes a contraindication in patients with hypersensitivity to the active substance(s) or to any of the excipients, in certain situations (e.g. penicillin allergy) patient safety would benefit if warnings regarding hypersensitivity were also present on the immediate packaging/label.

Examples of additional risk minimisation

The most common form of additional risk minimisation is educational materials for intended users, e.g. HCPs, caregivers and patients. Other approaches may also be considered in agreement with national competent authorities (e.g. educational videos showing correct reconstitution and injection of a solution, demo-kits for complex devices, pre-printed tables of calculations of weight and dose or rate to minimise calculation errors). Educational materials are predominantly paper-based but as risk minimisation evolves it is likely that MAHs will consider supplementing such materials with internet-based activities. New technologies in prescribing and dispensing systems to improve safe medication practice, such as smart phone applications, bar-coding and pill identifier websites are increasingly used. The use of the internet and such technologies should be discussed and agreed with national competent authorities in all cases with input sought from the Working Group on QRD as necessary.

The development of additional risk minimisation materials should involve consultation with communication experts, patients and HCPs on the design and wording of educational material and that, where appropriate, it is piloted before implementation. Such measures may also be subject to additional pharmacovigilance activities to monitor their effectiveness.

6.1.1. Error prevention through naming, packaging and labelling (including name review activities and use of colour)

6.1.1.1. Naming

Look-alike and sound-alike names of medicinal products which could pose a risk to patients' safety should be avoided. The name of a medicinal product can be an (invented) name, which is not liable to cause confusion with another (invented) name or a common name (e.g. international non-proprietary name (INN) or a common/scientific name), or a common/scientific name accompanied by trade mark or name of the MAH.

International non-proprietary name

The World Health Organisation (WHO) has issued guidance on devising new INN to facilitate the identification of pharmaceutical substances (active pharmaceutical ingredients), including the following recommendations.

- INNs should be distinctive in sound and spelling. They should not be inconveniently long and not be liable to confusion with names in common use;
- the INN should utilise common stems for products which are in related pharmaceutical classes (e.g. *-azepam* for diazepam derivatives, *-bactam* for beta-lactamase inhibitors). A list of all stems can be found on the WHO web site¹⁸;

¹⁸ <http://www.who.int/medicines/services/inn/stembook/en/>

- to avoid confusion, (invented) names should not be derived from INNs nor contain common stems used in INNs.

It is also important to consider the potential for confusion between products due to similarities in the INN. Confusion can arise from phonetic (sound-alike), orthographic (look-alike) and cognitive errors. There have been instances where products with similar INNs have been inadvertently used (e.g. prochlorperazine prepared instead of promethazine).

(Invented) name and name-setting 'INN/common name + MAH/trade mark'

The CHMP has issued guidance on the acceptability of names for human medicinal products processed through the centralised procedure¹⁹. The MAH/applicant should take this guidance into account when proposing names to the competent authorities.

For centrally authorised medicines, the potential for name-related medication errors that may occur at any level of the medication use process (i.e. prescription, dispensing, storage, preparation and administration) is assessed by the EMA's Name Review Group (NRG), on the basis of the guideline on the acceptability of names for medicinal products processed through the centralised procedure. The NRG assesses the degree of orthographic and/or phonetic similarity and the risk of cognitive error in the suggested name compared with already approved names. Taken into account in the assessment is the setting of use and elements that may increase or reduce the risk of confusion such as the strength and pharmaceutical form of the product. The potential for harm in case of accidental mix-up is also a part of the assessment.

Amongst others, this comprehensive review aims to ensure that proposed names

- do not lead to confusion in print, speech and handwriting with the names of other medicinal products or cause confusion in identifying medicinal products;
- do not convey misleading therapeutic/pharmaceutical connotations or are misleading with regards to the composition;
- are not promotional;
- do not create difficulties in pronunciation or have inappropriate connotations in the different EU official languages.

For certain medicinal products for which an INN is not applicable (e.g. vaccines), the common name should be based on the title of European Pharmacopoeia monograph if available. Common names for new vaccines should provide the appropriate information to facilitate the identification of the vaccine by HCPs.

6.1.1.2. Labelling and packaging

The aim of good labelling is the correct description of the medicine, clear product selection and identification, information ensuring the safe storage, selection, preparation, dispensing, and administration as well as tracking and tracing of the product. The design of labelling and packaging may lead to mis-selection of a medicinal product. Therefore all medicinal products placed on the market are required by Community law to be accompanied by labelling and PIL which provide a set of comprehensible information enabling the safe and appropriate use of the product.

Articles 54–57 and 61–63 of Directive 2001/83/EC specify the information which must appear on the outer packaging (or immediate packaging where there is no outer packaging), including the name of

¹⁹

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167844.pdf

the medicinal product, dosage unit, pharmaceutical form, list of excipients, method/route of administration, warning that the products should be kept out of the sight and reach of children, expiry date, batch number, contents by weight, by volume or by unit requirements, special storage or disposal conditions, and information in Braille.

The use of the QRD template ensures that the product is labelled with this minimum information and this can help to clearly identify the product and reduce the risk of confusion with other products. The readability guideline²⁰ provides guidance to ensure that the information presented is accessible and understandable. In addition, several organisations have published guidance for designs for safety (such as the NHS²¹) and recommendations to improve the safety of naming, labelling and packaging of medicines marketed in Europe (by the Expert Group on Safe Medication Practices²²).

On the printed outer packaging material, an empty space should be provided for attaching the prescribed dose. The special space constraints on small containers (e.g. vials) and blister packs should also be taken into consideration.

Use of colour

Colour differentiation can help to reduce the risk of product-selection errors within a manufacturer's product line when properly used, if such colours can be clearly distinguished from one another by the majority of users. However, this must take into account that red-green colour vision deficiencies affects up to 1 in 12 men and 1 in 200 women. The ISMP has issued guidance²³ which highlights the potential uses of colour e.g.

- colour coding, where there is a standard application of colour to aid in classification and identification;
- colour differentiation, which makes certain features stand out, or helps to distinguish one item from another;
- colour matching, where colour is used to guide matching up of various components of multi-part medicinal products.

However, in line with other guidances^{24,25} it is emphasised that the use of colour-coding is not usually recommended given the limited range of available colours and the absence of common understanding of colour coding conventions.

Different MAHs and applicants make use of colour as part of their brand and livery and in most cases there is no set colour scheme that must be used for a given indication or class of medicinal products. However, choice of colour should be considered in product design to ensure that it does not introduce the risk of confusion with other established products where informally-agreed colour conventions exists (e.g. in some Member States, asthma reliever inhalers have blue-coloured dust caps while maintenance corticosteroid inhalers have red or brown dust caps).

Products with the same manufacturer

MAHs may adopt packaging and labelling which supports a common "trade dress" and this can serve as an identifying mark and to create visual associations between multiple products from the same manufacturer. However, this assumes perfect performance by both HCPs and patients and it is therefore important to assess such trade dress to determine whether it may give rise to a risk of

²⁰ http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf

²¹ <http://www.nrls.npsa.nhs.uk/resources/collections/design-for-patient-safety/>

²² http://www.coe.int/t/e/social_cohesion/soc-sp/Medication%20safety%20culture%20report%20E.pdf

²³ <http://www.ismp.org/newsletters/acutecare/articles/20031113.asp>

²⁴ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

²⁵ http://www.edqm.eu/medias/fichiers/Report_2006.pdf

medication error and ensure that it does not compromise other distinguishing features of the medicinal product.

If a MAH markets two or more products in the same therapeutic area which have a similar company trade dress, the possibility of mix-ups between the medicinal products should be considered (and labelling amended accordingly).

There may be other key data elements which are important to emphasize visually on the outer packaging and on the medicinal product itself, to prevent mix-ups. For products associated with a high risk of medication errors, it may be important to consider including important information on this risk on both the primary and secondary packaging. For products available in different strengths, and where the consequences of under- or over-dose are potentially severe, it may be necessary to highlight the different strengths by use of increased font size and a warning colour such as red (noting the provisions for those with red-green colour blindness). Other measures may include the use of a 'hatching' effect to differentiate one similar product from another, or the introduction of a warning label to draw attention to critical information (e.g. "CAUTION HIGH STRENGTH").

Products with different manufacturers

In addition to the review of names and packaging, MAHs and applicants should consider the appearance and name of their medicinal product in comparison to medicinal products from other manufacturers used in similar indications, and the potential for confusion between medicinal products. This is particularly relevant for vaccines which are generally stored together in refrigerators in the local surgery and where the potential exists for accidentally selecting the wrong product due to similarities in appearance between medicinal products, and is also relevant for medicinal products which may be stored in the patient's fridge at home, such as injectable insulin products made by different manufacturers.

Use of illustrations and pictures in product information

Product information often includes illustrations of the use of the product or reconstitution prior to use. The MAHs and applicants should consider on a case-by-case basis whether it is clearer to use photographs or diagrams/pictograms to illustrate correct use of a product within product information. Any descriptions which accompany pictures should describe clearly only what is shown in the picture. As mentioned in section 5.1.3.2. , human factor testing can be very useful in demonstrating that instructions for use can be understood and followed without error.

Non-prescription medicinal products are likely to be used without the supervision of a HCP and labelling should therefore include all relevant information for the lay reader about safe use of the medicinal product. This includes use of diagrams and pictograms and advice on seeking medical help if there are any concerns. The acceptability of pictures, pictograms or diagrams as part of the product information of non-prescription products should always be assessed by national competent authorities.

6.1.2. Risk minimisation tools and activities

6.1.2.1. For patients/caregivers

Key to risk minimisation and prevention of medication errors is the provision of a suitable PIL which describes the correct use of the medicinal product. There is a requirement to include a user-tested PIL in the packaging of the medicinal product in most cases. However, it is important that large-print and Braille leaflets are also made available, particularly for patients with sight problems.

There is increasing use of the internet to provide information concerning medicinal products, for example, training materials for the insertion of etonogestrel contraceptive implants are provided on the

MAH's website to complement formal training and are intended to minimise the risk of medication error through incorrect insertion. Additionally, regulatory agencies may publish guidance on their websites on practices to reduce the risk of medication error. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK included an article in its drug safety update bulletin highlighting that insulin degludec was available in additional higher strength than existing insulins and that care was needed to minimise risk of error, including training for patients²⁶; the EMA has published guidance to ensure the safe and effective use of products to reduce the risk of medication errors e.g. Strensiq²⁷.

6.1.2.2. For Healthcare Professionals

HCPs are responsible for ensuring that patients are prescribed and receive the appropriate medication without errors. Where patients are responsible for self-administration of the medication, HCPs should ensure that the patient understands how to self-administer the medications appropriately in order to minimise the risk of medication errors. The provision and availability of suitable materials to facilitate discussions between HCPs and patients (or caregivers) is essential in this regard. For products provided in bulk to hospitals, MAHs may consider supplying multiple copies of the PIL or Technical Information Leaflet (TIL) so that each user can be provided with a copy.

Prescribers

Prescribers have an important role in determining that the treatment is appropriate for the patient, based on the licensed indication as described in the product information. Where products will be self-administered by patients, the prescriber has an important role in guiding the patient or caregiver on modalities of preparation and administration in order to avoid potential medication errors.

Pharmacists

Pharmacists may play an important role in verifying that the treatment is appropriate for the patient and that the patient has been informed of the safe use of the medicine and of any special instructions for the preparation or administration of the product. Pharmacists are also well placed to counsel patients at the point of dispensing on the use of their medications, including dose regimen, timing of medicine intake in relation to other medicines or food and use of devices such as inhalers, and to answer any questions from patients.

Some common dispensing errors identified in hospital pharmacies²⁸ include:

- dispensing the wrong medicinal product;
- dispensing the wrong drug strength;
- dispensing the wrong quantity;
- dispensing the wrong dosage form;
- dispensing the product with the wrong PIL or no PIL;
- dispensing with the wrong verbal information to the patient or representative.

For some of these errors, the risk may be increased for medications with similar names ((invented) name or name-setting INN+MAH/trademark) or similar packaging, medicinal products which are available in multiple strengths and or formulations, including different administration devices, and

²⁶ <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266132>

²⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/06/WC500188800.pdf

²⁸ Br J Clin Pharmacol. Jun 2009; 67(6): 676–680.

situations where the same active ingredient is present in different medicinal products for different indications.

6.1.3. Criteria to assess effectiveness of error prevention during post-marketing

The difficulties around standardised coding for medication errors in spontaneous reporting systems means that such systems are unlikely to be able to collect all incidents of medication error and will not collect reports of 'near misses'. There are a number of International Classification of Diseases (ICD) codes which relate to medication errors and which may be useful in the collection of data in this area. There is variety across Member States in the extent to which the reporting of adverse incidents is regulated by law. In some Member States, the reporting of adverse incidents is mandatory for HCPs and/or healthcare organisations, while in others, it is voluntary.

Collaborations between different national reporting systems which collect data on medication errors, regardless of whether or not they were associated with clinical consequences, are an important source of both process and outcome data. For medication errors associated with adverse reactions, the exchange of information is a legal requirement. Article 107a (5) of Directive 2001/83/EC states that the EU Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that EU Member State. They shall also ensure that the authorities responsible for medicinal products within that EU Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004. Reporting requirements for MAHs and national competent authorities for medication errors without ADR are addressed in the good practice guide referred to in section 5.1.1.

Routine pharmacovigilance through monitoring of spontaneous reporting systems is the most commonly-employed method of measuring the outcome of risk minimisation activities. However, spontaneous reporting systems have limitations and where further characterisation of the risk of medication errors is required (i.e. when and how medication errors occur) other methods of monitoring beyond spontaneous reporting systems should be considered.

A post-authorisation safety study (PASS) can be a useful method to show how patterns of use or reporting of errors may have changed following safety communications or changes in product labelling, and may also identify sources of medication in the post-approval setting. A number of examples of medication errors characterised further through PASS are included in Annex 3.

Another commonly employed method to measure the outcome of risk minimisation activities is a survey or questionnaire used to ascertain the retention and implementation of key risk minimisation messages by HCPs and/or patients. Survey approaches can be highly susceptible to recall bias on the part of the interviewees and therefore such studies require careful design.

Further guidance on the selection of risk minimisation tools and the measurement of the outcomes of these measures is provided in GVP Module XVI on risk minimisation measures: selection of tools and effectiveness indicators²⁹; guidance on the key elements of survey methodology is included as an appendix to GVP Module XVI.

²⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf

6.2. Specific considerations in high risk groups

6.2.1. Paediatric patients

The reflection paper on formulations of choice for the paediatric population (EMA/CHMP/PEG/194810/2005) suggests a range of approaches to the development of paediatric formulations³⁰ and the guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) offers guidance on the aspects of the pharmaceutical development of a paediatric medicine which are specific to these patients³¹.

Paediatric patients may be at particularly high risk of medication errors, with dosing errors representing the most common type of error (Ghaleb et al, 2006³²). This may relate to the variation in age, size and weight, body surface area (BSA) and degree of development in this population. Overdose was the most commonly reported medication error (accounting for 21% of all reports) in a study of paediatric patients (Manias et al 2013³³) while underdosing in certain paediatric specialties was the most commonly reported medication error in these settings (Bolt et al 2014³⁴). These conflicting findings indicate a more general risk of dosing errors (leading to either over- or underdosing) in paediatric patients. Paediatric prescribing is often determined by the patient's weight, yet weight is not measured before each prescription and can change over time meaning that periodic recalculation of drug doses is required. Due to the need to find the right dose based on weight (or BSA) for many of paediatric medicines, mathematical miscalculations may be more likely in paediatric patients than adults. The inclusion of charts with pre-calculated dose from strength and body weight in the SmPC, as appropriate, may be employed to avoid calculation errors.

The stakeholder workshop on medication errors noted that the risk of medication errors is particularly high in specific paediatric groups such as neonates, where age-specific dosing requirements are based on the known influence of ontogeny on the disposition of drugs. The weight of neonates may change rapidly over a short period of time, making the appropriate dose adjustment critical. Differences in the pharmacokinetic profile of neonates compared to that of older children probably contribute significantly to them being at higher risk of overdose (or underdose) and being less able to tolerate a medication error than older patients. This is largely due to the still developing hepatic enzyme systems and renal systems, vital for metabolism and clearance, as well as the variable absorption, delayed gastric emptying and reduced gut motility in neonates.

Occasionally there is a need for complex dilutions by HCPs; medication errors with infusion of fluids and electrolytes are common. For liquid oral medications (a formulation commonly used in children), particularly those which are viscous, there is some evidence that an oral syringe may be the most accurate dosing device³⁵. However, liquid formulations may present a risk for medication errors if an inappropriate dosing device is used to deliver them. The risk of mix-ups between different strengths of liquid oral medicinal products can be reduced by ensuring the different strengths have a different appearance and are presented in different packaging to each other.

Historically there has been a lack of development of paediatric medicines and lack of clear guidance on paediatric dosing in product information or other sources, leading to off-label use of medicinal products with indications in adult populations. The situation has improved with the introduction of Regulation

³⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

³¹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf

³² Ghaleb A, Barber N, Franklin B, Yeung V, Khazi Z, Wong I (2006) Systematic review of medication errors in paediatric patients. *The Annals of Pharmacotherapy* 40: 1766-1776.

³³ Medication errors in hospitalised children. Elizabeth Manias, Sharon Kinney, Noel Cranswick, Allison Williams. *Journal of Paediatrics and Child Health*. 01/2014; 50(1): 71-7

³⁴ Bolt R et al, *Journal of Clinical Pharmacy and Therapeutics*, 2014, 39, 78–83

³⁵ Padden Elliott J et al, Influence of Viscosity and Consumer Use on Accuracy of Oral Medication Dosing Devices *Journal of Pharmacy Technology*, August 2014; vol. 30, 4: pp. 111-117

(EC) No 1901/2006 which places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population.

Consideration should be given to the prevention of accidental ingestion or other unintended use of medicinal products by children. A standard statement that medicinal products should be kept out of the sight and reach of all children is included on the labelling for all medicinal products and the use of child-resistant packaging may also be considered.

6.2.2. Elderly patients

Elderly people account for 34% of all written prescriptions and this population is at high risk of medication errors. As noted in the concept paper on the need for a reflection paper on quality aspects of medicines for older people (EMA/165974/2013)³⁶, elderly patients may face physical and cognitive impairment and hence they may have difficulties in taking their medicines, e.g. swallowing tablets, opening packaging or reading the user instruction and package leaflet. The pharmaceutical development of medicines for use by older patients should take such aspects into consideration. Additionally, elderly patients frequently use multiple medicinal products (polypharmacy) which may in itself cause adherence problems which may be partly overcome by the pharmaceutical design of the medicines used (e.g. a wider range of colours, sizes and tablet shapes is known to assist the recognition of medicines and hence to reduce the risk of errors). Elderly patients are more likely to experience conditions which lead to impaired swallowing, such as stroke or Parkinson's disease. This can lead to accidental underdosing, which can be managed appropriately by the development and use of formulations which are easier for such patients to swallow.

Older patients (particularly those with diabetes) may be more likely to have impaired eye sight than younger patients, which may have implications for the correct use of insulin pens, in which case patients should be encouraged to get support from a caregiver.

It is important that appropriate materials for elderly patients are developed and user-tested, including use of large print text and Braille for patients with impaired eye sight. It is also important that MAHs do not rely solely on the provision of any additional information for patients via the internet, as elderly patients are less likely to be able to independently access such materials than younger patients.

Older people may also more frequently require the assistance of caregivers than the overall adult population. The caregiver, nurse and family can play an important role for the correct use of the medicinal product and should be involved pro-actively by the doctor or pharmacist. It is vital that elderly patients are asked explicitly what they want and how they feel about a prescribed medicinal product, rather than imposing a medication without considering the patient's circumstances and ability to use it safely.

6.2.3. Patients with visual impairment

GVP Module V highlights that when a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. The medicine most likely to be used by patients with visual impairment is eye drops and it is therefore critical that the font size used on eye drop containers is carefully considered given the small size of the container closure systems for such products. Article 56a of Directive 2001/83/EC makes clear that the name of the medicinal product must be expressed in Braille format on the packaging and MAHs shall ensure

³⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500141560.pdf

that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.

Where appropriate, medication errors related to visual impairment should be included as a safety concern in the RMP and appropriate risk minimisation measures proposed to address this risk.

6.3. General principles of good communication in relation to medicines information

For communication of safety information in the product information, the European Commission has issued guidance on the readability of the labelling and package leaflet of medicinal products for human use³⁷. The standard content and format of the PIL is defined in Directive 2001/83/EC and it should be designed in such a way as to be clear and understandable, enabling users to act appropriately, when necessary with the help of HCPs. The PIL should be kept updated and presented in line with the advice given in the QRD guidance on the content and format of these materials³⁸. The PIL should reflect all relevant information from the SmPC and be user-tested to show that users can find and understand information. The level of risk should be communicated clearly and side-effects should be assigned an appropriate frequency category. The use of the term "unknown" or "not known" in relation to frequencies of ADRs in the PIL is not useful to patients in helping them to understand the degree of risk, and may even raise alarm. For this reason, the MAH should attempt to designate a suitable frequency category for all ADRs in line with the guideline on the SmPC³⁹.

In 2003, the Committee of Experts on Pharmaceutical Questions created the Expert Group on Safe Medication Practices to review medication safety and to prepare recommendations to specifically prevent adverse events caused by medication errors in European health care. The Expert Group⁴⁰ has made a number of recommendations about communicating medicines information to patients. Key to these recommendations is the need to ensure that patient information and format is tailored to those who will receive it and their health literacy levels, not only to adult "standard" consumers. Large-print versions of the PIL should be made available on request for partially-sighted people while formats perceptible by hearing should be provided for blind people (although Braille may be appropriate in some cases). The Expert Group also made recommendations on the importance of patient counselling (as the PIL can be lengthy and is often not read).

It is also important to consider communication on medicines safety for HCPs. This is largely based on information presented in the SmPC, which provides essential information on the safe use of the medicine and can be used to describe the nature of any medication errors which may occur. When the risk of medication error and the need for additional communication tools has been identified, educational materials and/or direct healthcare professional communications (DHPC) may highlight key safety information which is important for the prescriber or treating HCPs to be aware of. However, these materials must reach the appropriate users and full use must be made of these materials in order to minimise risk. It is important that a comprehensive communication plan is agreed between MAHs and competent authorities which a) identifies the recipients of the information and b) describes the timing for dissemination of such materials. In some circumstances it may be more efficient to disseminate information through professional bodies rather than directly to HCPs and this should be considered as an option. The effectiveness of these additional measures should be captured and analysed in the PSURs and RMP.

³⁷ http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf

³⁸ http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf

³⁹ http://ec.europa.eu/health/files/eudralex/vol-2/c/smcp_guideline_rev2_en.pdf

⁴⁰ http://www.coe.int/t/e/social_cohesion/soc-sp/Medication%20safety%20culture%20report%20E.pdf

At a European level, the SCOPE Joint Action has a dedicated work package⁴¹ which is focussing on risk communications about medicines. Information will be collected on risk communications practice in the EU network to understand the communication channels and tools used, with frequency, strategy, and engagement approaches. A study will also be conducted on the knowledge, attitudes and preferences of target audiences towards different communications tools and channels in Member States to determine the effectiveness of different risk-communication methods. This will be used to develop a series of recommendations in the form of a communications toolbox including guidance for the media on scientific risk communication. There will be a particular focus on web portals and development of guidance (informed by the above activities) on the preparation of information for web portals, successful presentation and coordination of information on these platforms in the EU network. Delivery of the toolbox to EU Member States will be supported by training.

7. Operation of the EU regulatory network

As described in GVP Module VI on management and reporting of adverse reactions to medicinal products, reports of medication errors associated with harm are subject to the normal reporting rules as for individual case safety reports (ICRS).

It is also important that a learning culture is developed through the reporting of medication errors, even if these do lead to adverse outcomes. To this end, medication errors not associated with harm should be discussed in the PSUR and notified as an emerging safety issue if there is an impact on the benefit-risk balance of the product. Detailed guidance on the reporting requirements for medication errors and intercepted errors (or near misses) is provided in the good practice guide referred to in section 5.1.1.

7.1. Competent authorities in Member States

Article 107a of Directive 2001/83/EC imposes a legal obligation on EU Member States to record and report suspected adverse reactions that occur in its territory which are brought to its attention from HCPs and patients. For this purpose Member States operate a pharmacovigilance system to collect information on the risks of medicinal products with regard to patients' or public health, including suspected adverse reactions arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure (Directive 2001/83/EC, Article 101 (1)). This includes suspected adverse reactions arising from errors with human medicinal products.

EU Member States should also take all appropriate measures to encourage patients, doctors, pharmacists and other HCPs to report suspected adverse reactions, including those arising from medication errors, to the national competent authority (Directive 2001/83/EC, Article 102). For this purpose patient reporting should be facilitated through the provision of alternative reporting formats (i.e. through various media) in addition to web-based formats which Competent Authorities provide on their national websites.

It is particularly important that awareness of this reporting mechanism is raised amongst patients at a national level and national competent authorities should work with national patient safety organisations (PSO) to facilitate this. There are a number of critical factors essential to stimulate reporting from patients, including clarity about what to report and how, including a feedback mechanism to encourage further engagement.

⁴¹ <http://www.scopejointaction.eu/work-packages/wp6-risk-communications/>

Article 107a (5) of Directive 2001/83/EC outlines the key responsibilities of national competent authorities in relation to the reporting of ADRs associated with medication error:

Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the EudraVigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.

Furthermore, EU Member States have an obligation to evaluate the information held in their pharmacovigilance system scientifically, to detect any change to a medicine's benefit-risk balance, to consider options for risk minimisation and prevention and to take regulatory action concerning the marketing authorisation as necessary. The general responsibilities of competent authorities in relation to risk management are outlined in GVP Module V and apply likewise to the management of medication errors.

National competent authorities should record and report all suspected adverse reactions in line with the requirements set out in Article 107a of Directive 2001/83/EC.

7.2. Pharmacovigilance Risk Assessment Committee

Article 61a (6) of Regulation (EC) No 726/2004 outlines the mandate of the Pharmacovigilance Risk Assessment Committee (PRAC) which shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post- authorisation safety studies and pharmacovigilance audit.

The PRAC shall be responsible for providing recommendations to the Committee for Medicinal Products for Human Use (CHMP) and the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMD-h) on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems and it shall be responsible for monitoring the effectiveness of those risk management systems (Article 56 (1)(aa) of Regulation (EC) No 726/2004).

This includes any risk minimisation measures to prevent or minimise the risk of medication errors, including the assessment of their effectiveness in line with the provisions of GVP Module XVI.

7.3. Patients and healthcare professionals

The stakeholder workshop on medication errors called for pro-active engagement and capacity building with patient consumer groups and HCPs on a systematic basis to improve safe medication practices. MAHs may consider consulting patients, HCPs but also caregivers and other healthcare providers (depending on the healthcare delivery system where the medicinal product is intended to be used) on the design, user testing and communication strategy of risk minimisation measures. This can be helpful in ensuring that risk minimisation measures tailored to prevent or minimise medication errors are effective in practice.

Patients and HCPs should not report medication errors resulting in adverse reactions via both the marketing authorisation holder and the national pharmacovigilance reporting scheme, but rather in

accordance with the reporting requirements applicable in the relevant Member State for which the information is provided in the PIL of the medicinal product.

7.4. Marketing authorisation applicant or holder

MAHs are required to operate a pharmacovigilance system for the fulfilment of pharmacovigilance tasks equivalent to the relevant EU Member State's pharmacovigilance system. This includes the obligation to collect and collate all solicited and unsolicited reports of suspected adverse reactions, including those arising from errors with human medicinal products, and to evaluate all information scientifically, to consider options for risk minimisation and prevention and to take appropriate measures as necessary. As part of the pharmacovigilance system, the marketing authorisation holder shall operate a risk management system for each medicinal product and monitor the outcome of risk minimisation measures which are contained in the RMP or which are laid down as conditions of the marketing authorisation (Article 104 of Directive 2001/83/EC), including those required to prevent or minimise the risk of medication errors.

In line with the recommendations of GVP Module VII medication error reports not associated with an adverse drug reaction should be included as a summary in the PSUR sub-section VII.B.5.9 2. 'Medication errors'. This summary could include relevant information on patterns of medication errors and potential medication errors based on periodic line listings of case reports which should be made available by MAHs on request of the national competent authority or the Agency.

In line with the recommendations of GVP Module V the potential for medication errors should be discussed e.g. based on a summary of aggregated data on medication errors which occurred during the clinical trial programme and/or post-marketing period.

It is important that MAHs systematically collect and evaluate scientifically reports of medication errors which are brought to their attention which do not fall in the definition of a reportable ICSR (i.e. intercepted errors, medication errors without harm and potential errors). MAHs should integrate relevant information about the category (type) of error, the stage of medication process where the error occurred, any contributing factors (e.g. human factors, healthcare system factors or external factors) and mitigating factors (e.g. actions or circumstances which prevented or moderated the progression of an error towards harming the patient) in the evaluation of the risk for the patient and the appropriate risk minimisation measures(s). Further guidance is provided in the good practice guide referred to in section 5.1.1.

7.5. European Medicines Agency

Within the EU, the responsibility for authorisation and supervision of medicinal products is shared between the national competent authorities in EU Member States, the European Commission and the Agency, with the balance of responsibilities depending upon the route of authorisation.

For centrally authorised products Article 107 (1) of Directive 2001/83/EC requires the Agency in collaboration with EU Member States to monitor the outcome of risk minimisation measures contained in the RMPs and of the conditions of marketing authorisation (particularly those for the safe and effective use), to assess updates of the RMP and to monitor the data in the EudraVigilance database to determine whether there are new risks or whether the risk have changed and whether those risks impact on the benefit-risk balance (Article 107h (1) of Directive 2001/83/EC). Also MAHs, national competent authorities and the Agency shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance.

These provisions apply to any safety concern including medication errors identified in a RMP for a medicinal product regardless of the route of authorisation.

List of acronyms

ADR	Adverse reaction
AE	Adverse event
BSA	Body surface area
CHMP	Committee for Human Medicinal Products
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
DHPC	Direct healthcare professional communication
DSUR	Development safety update report
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FMEA	Failure mode and effects analysis
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
ICD	International Classification of Diseases
ICH E2E	International Conference for Harmonisation E2E standard
ICSR	Individual case safety report
IM	Intramuscular
INN	International non-proprietary name
ISMP	Institute for Safe Medication Practice
ISO	International Standards Organisation
IV	Intravenous
MAH	Marketing authorisation holder
ME	Medication error
NCA	National competent authority
NRG	European Medicines Agency's Name Review Group
PASS	Post-authorisation safety study
PCA	Perception-cognition action
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Package leaflet (patient information leaflet)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PUMA	Paediatric use marketing authorisation

QRD	Quality Review of Documents
RCA	Root cause analysis
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
TIL	Technical information leaflet

Annexes

Annex 1 – Potential sources of medication error in medicinal product design

Tablets

- Some multiple tablet strengths are available with a similar appearance in terms of colour, size and shape (or if multiple strength tablets are presented in similar packaging to each other), which may lead to incorrect dosing.
- A product is available in immediate-release and modified-release formulations but the packaging and tablet appearance are similar, which may lead to overdosing.
- Some tablets include a score-line down the centre so that tablets can be broken into smaller doses, but the tablets may be difficult to break or not break cleanly, meaning that broken tablets may not provide the correct dose.
- Tablets which are not suitable for breaking (such as those with an enteric coating or controlled-release coating) may be broken or cut and used by patients.
- The size of a tablet may make the medicinal product difficult to swallow for some patients and tablets may be irritating to the oesophagus.
- Tablets are usually presented within foil-sealed blisters or within foil pouches but tablets may break (particularly if brittle or fragile) if pushed through the foil too hard; this can be problematic if only part of the tablet is taken or if the tablet should not have been crushed/broken (e.g. modified-release preparations).
- Blister packs may be difficult to open for patients with dexterity problems.
- Some formulations are developed for oral administration but should not be swallowed at all or not directly, for example sub-lingual tablets, buccal tablets, melts and oro-dispersible tablets. These dissolve in the mouth, under the tongue or inside the cheek but may not dissolve quickly or could be inadvertently swallowed instead of slowly dissolving, which may affect absorption and efficacy.
- Some tablets are presented as soluble, dispersible or effervescent formulations which must be fully dissolved in water before administration, but attempts may be made to dissolve these (unsuccessfully) in liquids other than water.
- Medicines are sometimes packaged with a desiccant and there is a risk that patient may accidentally mistake this for a tablet and ingest it.

Capsules

- Capsule shells are often made of gelatine which can become brittle if exposed to air for a long time or if the foil is removed from blister packs too far in advance of use of the capsule.
- Capsules may be opened where this is not intended and the contents sprinkled onto food, but this may not be appropriate where the capsule contents may be irritating to the oesophagus.
- A number of respiratory medicinal products are presented in capsule form for inhalation of the capsule contents through a device; such products may inadvertently be swallowed by patients.

Oral solutions and suspensions

- The wrong dose may be obtained in situations where multiple liquid medicine strengths are available but presented in similar packaging and have a similar appearance in terms of colour and flavour.
- Solutions or suspensions may require use of dosing devices and these can be associated with problems; liquid medicinal products measured into plastic dosing spoons can develop a meniscus which can lead to overdosing.
- Liquid formulations are likely to be presented with child-resistant closures to reduce the risk of children accidentally ingesting the medicine within but these can be difficult to open for patients with manual dexterity problems.
- Suspensions require shaking to produce a homogenous suspension before dosing and this is not always made clear.

Other orally administered formulations

- Some dose forms have been developed for ease of use or administration but these may present hazards. These include dose forms such as lozenges with integral oro-mucosal applicator or which have been developed to be chewable and palatable, which could be mistaken for sweets by children. Similarly, medicated chewing gum may be mistaken for regular chewing gum which could expose users (and especially children) to potential harmful doses of the active ingredient.
- There may be accidental parenteral use of oral solutions if these are presented in a format such as a syringe, intended to assist with accurate oral dosing.

Patches

- Patches may be difficult to locate or identify in situ leading to inadvertent overdose if more patches are applied than is recommended or if patches are left on the skin for longer than directed.
- Pyrexia can increase exposure to the active ingredient in transdermal patches, which can be problematic if the patient is pyrexial during initial adjustment of dosage.
- Patches which are still pharmaceutically active may become accidentally stuck to people other than the patient (i.e. accidental exposure) if they fall off the intended wearer, or if they are stored or disposed of improperly.
- Patches may be adhered to non-recommended sites which may expose users to a higher dose than intended.
- Cutting patches into several pieces for ease of application may reduce the dose and efficacy or may cause the patch not to work at all, if the patch has been formulated in such a way that cutting it is not recommended.
- Patches with different modified release rates may cause medication errors if labelled using the name-setting "INN + MAH", which makes it more difficult to distinguish the different products from each other.
- There have been reports of patches containing metal as part of the adhesive backing causing skin burns when worn during MRI scans.
- There have been reports of elderly dementia patients removing the patch and chewing it.

Suppositories

- Non-parenteral formulations such as suppositories and pessaries may be accidentally eaten instead of being inserted, and may also be used at the wrong sites.

Topical products

- Eye drops are often presented in a bottle or individual single-use droppers but these can be difficult to hold and use for patients with manual dexterity problems.
- There have been examples of the tips of single-use droppers having sharp edges when broken open to use, which could damage the cornea.
- There may be confusion between products presented in small bottles and eye drops; there has been an example where decongestant oil (e.g. eucalyptus) was administered inadvertently to the eye.
- For drops presented in multi-dose containers, instructions for use vary and patients may squeeze the bottle excessively and may deliver a larger amount of solution which could have a noxious effect on the surrounding skin of the eye.

Aerosols and inhaled medicinal products

- Some medicinal products are presented as an aerosol spray which could get into the eyes or irritate damaged or broken skin.
- A common error with orally inhaled medicines presented in aerosol form (a pressurised metered dose inhaler, pMDI) is patients' difficulty synchronising inspiration with inhaler activation; in this situation a full dose may not be inhaled and the medicinal product may be largely deposited in the mouth instead.
- Breath-actuated dry powder inhalers (DPI) rely on inspiratory airflow, and patients with poor respiratory airflow may find DPI difficult to use and they may be less efficacious than pMDI for such patients.
- There are a broad range of inhaler devices available and all differ in their design and function, giving rise to the potential for misunderstanding of their operation. Most pMDI require shaking of the container to mix, then pressing of a button to actuate while multiple dose DPIs require priming by pressing a button, sliding a lever or twisting the base of the inhaler.
- For multi-dose unit DPIs, the medicinal product inside is regularly replaced. Where devices do not have a dose counter available it can be difficult to tell when the inhaler is empty.
- There are a range of inhaler spacer devices available, and these are not compatible with all inhalers. Spacers may accidentally be used interchangeably, leading to errors of dosing.
- Inhalers frequently have a dust cap in place to protect the mouth piece but if this is absent, foreign bodies may enter the mouthpiece of the inhaler and be inhaled or swallowed when the medicinal product is next used.
- Inhalers may stop working altogether if dropped accidentally.
- Medicinal products administered via nebulisers may accidentally get into the eyes if a face mask system is used, or the nebuliser may become contaminated if not cleaned properly or if the medicinal products used in it are not handled correctly.
- Some nebuliser solutions are presented in individual dose plastic containers. These may be described as "nebules" on the packaging, but some are described as "ampoules" for inhalation use.

This later description may lead to inappropriate administration as ampoules are generally regarded as containing medicines for injection.

Parenteral medicinal products

- Parenteral products which require dilution before use may be presented in an apparently ready-to-use form and could lead to use of a concentrated dose. Some medicinal products require a number of diluting steps to achieve the final solution for injection (e.g. mycophenolate mofetil requires a reconstitution step followed by a dilution step, both with 5% Glucose, prior to use) which increases the number of stages at which errors in dilution could be made.
- Products requiring reconstitution are often presented as a powder or concentrate along with a solvent/diluent and it is possible that a concentrate-solvent mixture with an unintended concentration may be achieved if the wrong amounts of concentrate and diluent are mixed. This can particularly occur if the solvent vial and the concentrate vial each contain an overfill to compensate for liquid lost during the initial dilution process but where the contents are not entirely mixed.
- There may be confusion over appropriate dosing in situations where there are difficulties calculating the correct dose in mg/ml or ml/kg for solutions presented as a w/v% concentration.
- There are problems if the strength on ampoule labels is provided as concentration, e.g. in mg/ml, but the total content of active substance in the ampoule is much higher (or much less). If the medicine is used without recalculation or reading the label text carefully, over- or underdosing may occur.

Errors due to presentation of the medicinal products

- The container closure system may be a source of error if solutions intended for topical or oral use are mistaken for products for injection.
- Some medicinal products are presented in a ready-to-use syringe but the potential for medication errors can arise if multiple strengths of a product are presented in a syringe with an identical fill volume.
- For penicillin-containing products, especially vials which are presented in boxes of 10 with only one package insert, this insert is sometimes removed leaving no other obvious means of identifying the product as a penicillin if there is no warning on the box/vial labels; this introduces the risk of inadvertently exposing patients with penicillin allergy to this product.

Examples of medication error due to invented name mix-ups and other naming confusion

- There have been cases where Diamox (acetazolamide) has been mistaken for Zimox (amoxicillin trihydrate).
- In some Member States, confusion arose between the invented names Lasix (furosemide) and Losec (omeprazole) which may look similar when handwritten.
- There have been cases of product name confusion between Plavix (clopidogrel) and Pradaxa (dabigatran etexilate), particularly as both products have a 75mg dosage form and daily posology.
- There has been confusion between the invented names Faustan (diazepam) and Favistan (thiamazole); consequently the MAH changed the invented name of the diazepam medicinal product to *Diazepam Temmler* to reduce the risk of medication error due to mix-ups between the two medicinal products.

- A hospital in-patient's dose of levetiracetam was delayed because the company name was included as part of the drug name all on one line, and the hospital staff were unsure what the significance of this was and whether it was usual levetiracetam and not some unusual formulation.

Examples of medication errors due to wrong dose or errors in dose titration

- Dose calculation and infusion rate errors have been reported with tocilizumab, which has indications in rheumatoid arthritis, systemic juvenile rheumatoid arthritis and paediatric juvenile idiopathic polyarthritis with different doses and infusion rates required depending on the indication and weight of the patient; *educational materials were put in place for patients, nurses and physicians to emphasise that patients should be monitored for infusion-related ADRs.*
- Patients were mistakenly treated with immediate release tacrolimus instead of prolonged release tacrolimus which in some cases resulted in patients being dosed incorrectly, leading to serious adverse reactions including biopsy-confirmed acute rejection of transplanted organs. *Following these incidents, HCPs were reminded of the potential for mix-ups and the packaging was amended.*
- There was concern over the potential for incorrect dosing with pramipexole in situations where the immediate-release formulation was mistaken for the prolonged-release formulation; there was also the potential for accidental overdose if prolonged-release formulations were crushed for ease of swallowing. *Packaging was redesigned to differentiate between the two products and a warning was placed in the PIL for the prolonged-release formulation stating that the medicine must be swallowed whole and not chewed, divided or crushed.*
- A review of potential fatal overdose due to medication errors with methotrexate revealed that in many cases patients were receiving daily treatment instead of once weekly treatment; *a number of sections of the SmPC and PIL were updated to emphasise that methotrexate should be used once weekly.*

Examples of error due to reconstitution and administration

- Lack of effectiveness was reported with leuporelin suspension for injection due to errors in the preparation, mixing and administration of the product, requiring amendment of the instructions for use/reconstitution; *a Direct Healthcare Professional Communication and a communication plan to inform HCPs about the correct product reconstitution and administration and about the importance of the different steps was developed and the SmPC was updated to include a statement that "Lack of clinical efficacy may occur due to incorrect reconstitution of the product (see section 4.2)" and to allow storage of the product at room temperature for up to 1 month. The closure system was modified so that it will be impossible to remove the blue plunger rod without removing the grey stopper.*
- There have been reports of life-threatening overdose with a hybrid formulation of topotecan due to confusion arising from the hybrid having a higher concentration than the dilution concentration of other topotecan products; *this is clearly labelled in product information and a coloured vial collar acts as a strong visual reminder to notice the concentration.*
- There have been reports of inappropriate dilution of bortezomib which is reconstituted with differing amounts of solvent depending on the site of administration; *a dosing card, poster, leaflet and product information describe the correct dilution for administration by subcutaneous and IV routes.*
- Prescribing, dispensing and medication errors have been reported with olanzapine where the rapidly-acting intramuscular (IM) injection formulation has been confused with the prolonged-release depot formulation; *a HCP awareness programme is in place including a DVD, slides,*

brochure and patient alert card to explain the differences between the two IM formulations of olanzapine (including packaging differences).

- A product presented in two ampoules (one ampoule containing water as the solution for injection and the other ampoule containing the powder for solution) was labelled only with the invented name. This introduced the possibility for misunderstanding, because the ampoule with the solution may have been mistaken for the medicinal product containing the active substance and the patients may receive only water for injection. *The product was relabelled to make it clear that the ampoule containing the solution contained water for injection, for use with the active substance.*

Examples of medication error due to mix-ups based on product design and labelling

- A case of unintended pregnancy was reported when a product used to treat symptoms of menopause was dispensed in error as oral contraception due to similarities in the trade dress and a similar combination of ingredients as other oral contraceptives.
- Patients were mistakenly vaccinated with Repevax instead of Revaxis due to similarity in names, labelling and packaging; children over 10 years of age and previously unvaccinated children received a dose of pertussis in addition to the appropriate booster immunisation against diphtheria, tetanus and poliomyelitis. *The MAH amended the packaging for Repevax to help distinguish it more clearly from Revaxis and this change was also communicated to HCPs.*
- The presentation of different insulins in the same Flexpen device has led to reports of mix-up between these two insulins.
- In Denmark, there have been reports of mix-ups between Gardasil and MMR vaccines because of packaging being similar between the two products.
- Pharmacists raised concerns that a fixed-dose combination of vilanterol and fluticasone furoate with indications in the maintenance treatment of asthma and chronic obstructive pulmonary disease (COPD) may be used in error for the relief of symptoms of asthma due its presentation in an inhaler device with blue parts, blue being a common choice of colour for reliever inhalers in some EU Member States. *The colour of the dust cap on the inhaler was changed to yellow.*

Examples of medication errors involving administration devices

- Misplacement of intraocular implants has been reported and found to be due to mechanical failure of the implantation device; *this led to introduction of training materials for the use of the device.*
- Breakage of levonorgestrel intrauterine devices on removal has been reported, meaning that pieces of the device have been left in situ.
- Due to malfunction of the pre-filled pen device several patients were reported to have missed a dose of adalimumab, one of whom was hospitalised with flare-up of the underlying disease.
- A liquid oral formulation of paracetamol was presented with a dropper graduated in mL for infants less than 3 years and an oral syringe graduated in mL for infants older than 3 years; both products have similar labelling and the use of the large dosing device intended for children aged 3 to 10 years to prepare a dose for an infant could result in serious overdose.

Annex 2 – Design features which may reduce the risk of medication errors

Tablets

- In the case of applications for more than one tablet strength, the different tablet strengths should be distinguishable at a level sufficient to avoid mistakes between the different strengths by the final user. Distinguishing tablet strengths by colour/shape and marking/embossing is preferable.
- Colour conventions should be followed where these have been agreed at Member State level for a class or group of medicinal products; care should be taken in clinical trials where colours may be changed to preserve blinding.

Figure 1: Example for colour coding of different strengths of warfarin tablets in the UK.



- Tablets which are irritating to the oesophagus should be accompanied by instructions for use on how to avoid harm (e.g. for alendronate, patients are instructed to take the medicine with a full glass of water and instructed not to lie down afterwards).
- Where reports have been received of tablets being difficult to swallow (e.g. due to size or coating), reformulation or a break mark could be considered.
- Children may not be able or willing to swallow a medicinal product, even when the dosage form, the formulation or the preparation is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms, formulations or preparations to the market (e.g. oral liquid as well as tablets). When this is not feasible, alternative strategies for intake of the medicinal product should be discussed by the applicant.
- The instructions for handling of tablets/capsules which are friable and prone to breaking should instruct the user to peel back the foil covering blister packs and remove the tablet from the blister.
- The presentation of products in a range of strengths which do not increase tenfold can reduce the risk of mix-ups between strengths (e.g. rather than making available strengths of 1.25 mg and 12.5 mg, strengths of 3 mg and 20 mg, or 2 mg and 10 mg are made available).

Capsules

- Most capsule shells are made of gelatin but other materials (e.g. hypromellose) are available and may be more suitable and less prone to capsule breakage than gelatin, particularly if they encapsulate particularly hygroscopic substances.
- Labelling should highlight the importance of not exposing capsules to air (e.g. by removing from blisters) until they are administered, as well as not opening capsules before use (unless opening capsules is an approved way to use the medicine, e.g. sprinkling the contents on food).
- Respiratory medicinal products presented in capsule form should carry instructions on using the capsule with the approved inhaler device, that the capsule should not be swallowed and that only the approved inhaler device should be used to deliver the medicinal product.

Other orally administered formulations

- Medicinal products which dissolve on or under the tongue or in the cheek should be accompanied by instructions that the product is not intended to be swallowed and give direction on the length of time the medicinal product should be left in place.
- Medicinal products which may be mistaken for sweets are preferably packaged very plainly and should carry instructions to keep out of reach and sight of children.
- Effervescent products should always be fully dissolved prior to administration; when used in children it may be helpful to indicate the minimum volume an effervescent product can be dissolved/dispersed in as well as the solubility of the drug so that fractional doses can be given, if necessary⁴².
- For effervescent, soluble and dispersible preparations, clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing⁴³.
- For products presented as powders or multi-particulate formulations where the prescribed dose is mixed with a small amount of soft food or with a drink prior to administration, the product information should specify which commonly available foods are suitable for mixing with the preparation, and also list foods that should be avoided due to stability, compatibility or taste issues.

Patches

The guideline on quality of transdermal patches (EMA/CHMP/QWP/608924/2014)⁴⁴ includes guidance on a number of issues which may impact on the risk of medication errors highlighted below:

- Transdermal patch design should avoid cutting by patients or health care professionals and a smaller transdermal patch should be developed instead. However, in exceptional cases for good patient safety and efficacy reasons, cutting might be necessary. In such cases this should be described and supportive data should be provided in eCTD Module 3.2.P.2 as well as in the clinical dossier.
- The SmPC, package leaflet and labelling should fully address the correct administration of the transdermal patch and include any necessary warnings for the safe use of the drug product. Consideration should be given to the safety of medical personnel and patients after the use of the product, especially for controlled drugs (e.g. opioids).
- The suitability of the transdermal patch in use should be fully discussed in the marketing authorisation application. The following should be considered:
 - the identification, markings, appearance and visibility of the transdermal patch;
 - accidental dosing due to lack of visibility should be addressed;
 - site of administration, and change in site per dose;
 - the necessity to avoid damaged skin;
 - the requirements for skin pre-treatment;

⁴² http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

⁴³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf

⁴⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179071.pdf

- the administration and securing of the transdermal patch, including if applicable the use of an overlay;
- effect of exposure to environmental extremes of heat and cold;
- effect of normal human behaviour such as washing, showers, sleeping, use of sun screens and moisturisers;
- action to take in the event of adhesion failure, patch displacement or detachment, cold flow;
- accidental transfer of patches to the skin of a non-patch wearer (particularly a child);
- any necessary restrictions, e.g. metallised backing and magnetic resonance imaging (MRI), avoidance of occlusion;
- the practical suitability of any special storage conditions;
- avoiding appeal to and inadvertent use by children;
- avoidance of cutting of the transdermal patches;
- special precautions for disposal, e.g. used patches should be folded so that the adhesive side of the patch adheres to itself and they should be safely discarded and unused patches should be returned to the pharmacy.

Suppositories, pessaries and implants

- Suppositories and pessaries should be accompanied by instructions for use which state that they should not be swallowed or placed in the mouth.
- Instructions (including pictures) for handling, insertion, placement, checking of correct siting and removal of implants should be included in the product information.
- Implants can be reformulated to include tracers allowing for detection by x-ray or other means (e.g. Implanon was replaced with Nexplanon, which has had barium sulphate added to make it radio-opaque).

Solutions, suspensions and topically-applied liquids

- Measuring devices may be required to deliver oral, parenteral, nasal, vaginal, and rectal liquid dosage forms to patients. Liquid medicinal products can be marketed with an appropriate graduated measuring device, such as an oral or enteral dosing syringe (that cannot be connected to intravenous catheters or ports), dropper dosing cup, beaker or spoon.
- The suitability of the measuring device for the medicinal product should be considered, particularly with regard to: dosing accuracy and precision in relation to the therapeutic window of the drug substance; the risk of overdosing in relation to the measuring device; the physical characteristics of the liquid in relation to the measuring device⁴⁵.
- Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available⁴⁶.

⁴⁵

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0

⁴⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf

- Liquid medicines for use by patients who are likely to have manual dexterity problems (e.g. rheumatoid arthritis) can be easier to open when presented in containers with Medigrip lids; if child-resistant closures are necessary those with keys (which still allow ease of opening) can be used.

Eye drops

- The Quality of Medicines Questions and Answers (Part 2)⁴⁷ provide aspects which are relevant to reducing the risk of medication errors with eye drops:
 - the specification of plastic containers for eye drops for human use should include a qualitative test for surface defects such as excessive burrs and sharp edges around the dropper tips (and include tests for container opening characteristics including check for burrs and sharp edges after the container is opened);
 - the product information (SmPC, PIL, labelling) should include appropriate instructions based on the development data and studies undertaken, including the orientation of the bottle (e.g. inverted or inclined) and whether or not the bottle should be squeezed to dispense the product.
- Single-use products can be differentiated from multiple-use presentations by changes e.g. of the labelling, shape of the packaging, opacification or colouring of the packaging.

Aerosols and inhaled medicinal products

- The guideline on the pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/49313/2005 Corr⁴⁸) includes a number of aspects which are relevant to reducing the risk of medication errors. This includes that the SmPC should contain the following information:
 - for inhaled products, the instructions for use should be clearly described, including directions with respect to the following items (if applicable):
 - shaking requirements;
 - cold temperature use;
 - the need for priming and re-priming;
 - the effect of flow rate on the performance of the product;
 - orientation of the inhaler during inhalation;
 - the use of any specific spacer/holding chamber;
 - cleaning requirements, including instructions for any specific spacer/holding chamber.
 - for intranasal products, the instructions for use should be clearly described, including directions with respect to the following items (if applicable):
 - shaking requirements;
 - cold temperature use;
 - the need for priming and re-priming;

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000185.jsp&mid=WC0b01ac058002c2ab

⁴⁸ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf

- cleaning requirement.
- Dropping of the device should be investigated as part of the robustness study defined in the guideline on the pharmaceutical quality of inhalation and nasal products (section 4.2.18)⁴⁹.
- Inhaled medicines containing steroids should be accompanied by a recommendation to rinse out the mouth after use to reduce the risk of oral candidiasis.
- When a spacer or holding chamber is required for administration of the product to a particular patient population (e.g. paediatrics, administration of high dose steroids), its use should be validated. Relevant information on the spacer/holding chamber must be given in the SmPC. In addition to in vitro studies, the suitability of the spacer should be supported by appropriately designed clinical studies. For inhalers with removable dust caps over the mouthpiece, it is helpful to include a reminder in the PIL that the dust cap should be replaced when the product is not in use.
- Solutions for use with a nebuliser should be accompanied by instructions for use with various types of nebuliser (jet and ultrasonic); product information for products containing steroids or antibiotics and which are intended for use with a nebuliser should include a warning not to use with a facemask (in order to avoid contact with the eyes and skin of the face).

Products for IV use or parenteral administration

- The authorised route(s) of administration should be clearly stated in the product information.
- The product information should describe suitable solvents and diluents if supplied as a powder or concentrate for reconstitution.
- Where products consisting of a concentrate and solvent contain an overfill to compensate for liquid lost during the dilution process, labelling should indicate that the entire contents of the solvent vial must be added to the concentrate vial.
- Instructions for use for IV medicines should include instructions on the time over which the product should be administered or else a statement that a bolus dose may be given.
- Instructions for calculating dose when robots are used to dispense the product should be part of the SmPC.
- If a medicinal product has to be administered within a specific time after reconstitution or dilution this should be described in product information.
- Information on the appropriate dilution of solutions should be included in the SmPC and products requiring dilution require a TIL for use by HCPs to accompany the PIL; information on dilution should be described in the TIL (if applicable).

Warnings on the outer packaging of the product

There are a number of examples where additional warnings have been placed on the outer packaging to address specific medication errors:

- Advagraf prolonged-release hard capsules and Mirapexin/Sifrol prolonged-release tablets display the posology ('Once daily') in section 5 (method and route(s) of administration) as a way to address the medication errors reported due to mix-ups with the immediate release formulations (Prograf tablets and Mirapexin/Sifrol tablets).

⁴⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf

- Velcade and the bortezomib generics display 'Intravenous use only' (or 'Subcutaneous or Intravenous use only' for higher strengths) along with the statement 'Do not give by other routes' in section 5 (method and route(s) of administration) since medication errors were reported due to the use of Velcade intrathecally.
- In case of products containing desiccants, the statement 'Do not swallow the desiccant canister found in the bottle' has been added to Section 7 (Other special warning(s), if necessary).

General considerations

- MAHs should consider using "mL" as the standard unit of measure for measuring devices.
- Medicines for acute use in emergency situations are most usefully presented in a ready-to-use format without the need for measuring of doses or solutions.
- Where an active substance is available with different (invented) names or where different strengths have different indications, the product information should highlight any differences in
 - posology between the products (e.g. daily versus weekly administration of insulin analogues) or
 - composition (e.g. different excipients⁵⁰, some of which may cause allergies such as milk proteins or peanut oil).
- Ideally all penicillin containing products (including oral products) should include "contains penicillin" on the outer packaging/label.
- Biological products (including similar biological products) should be clearly differentiated from each other for the purposes of pharmacovigilance. The name and the batch number of the medicinal product given to the patient should always be recorded.
- Educational material and/or the SmPC should, when relevant, include calculation tables in which dose is calculated from 'mg per body weight' or 'mg per body surface' or 'mg per renal function' into the actual dose. This is particularly relevant for medicines intended for use in paediatric patients.
- For products used in a hospital or care home setting, consideration should be given to using tamper evident features (such as for emergency use pre-filled syringes, tubes/tubs of creams and ointments, inhaler boxes, and mouthwashes) to reduce errors relating to administration of a product to more than one patient.

⁵⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf

Annex 3 - Examples of medication error characterised further through PASS

- For aflibercept, the potential risk of medication errors due to overdose from the pre-filled syringe is being addressed by an observational PASS to evaluate physician and patient knowledge of safety and safe use information of aflibercept in Europe.
- Medication errors due to the incorrect application of rivastigmine patches were addressed by circulation of a DHPC but monitoring of cases reported through spontaneous reporting systems showed cases were still being reported with no clear trends of improvement observed after the DHPC was issued. Further risk minimisation measures to manage the risk of medication errors leading to overdose were implemented including updates to the product information and educational material for prescribers. To measure the success of these measures additional pharmacovigilance in the form of a drug utilisation study was required.
- For insulin lispro, the risk of medication errors potentially arising due to confusion with different presentations with different strengths is being targeted through dissemination of a DHPC and patient communication materials. A patients and physician survey will assess the effectiveness of the DHPC.
- For cabazitaxel, the risk of medication errors related to errors in reconstitution of the product led to dissemination of a DHPC and updates to product information in order to improve the readability of the information for reconstitution. The effectiveness of the DHPC is being conducted through a survey of hospital pharmacists.