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Good practice guide on risk minimisation and prevention of medication errors

Draft

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Comments should be provided using this template. The completed comments form should be sent to medicationerrors2013@ema.europa.eu by 14 June 2015.

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As part of the public consultation of the draft good practice guide on risk minimisation and prevention of medication errors the European Medicines Agency (EMA) would also like to take the opportunity to obtain stakeholder feed-back on the following questions:

1. With regard to chapter 5.2.5 would you consider the examples of medication errors resulting in harm during the post-authorisation phase useful taking into account the regulatory remit for risk minimisation measures?

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. To support operation of the new legal provisions amongst the stakeholders involved in the reporting, evaluation and prevention of medication errors the Agency in collaboration with the EU regulatory network was mandated to develop specific guidance for medication errors, taking into account the recommendations of a stakeholder workshop held in London in 2013.

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

1. Introduction (background)

A medication error is considered to be any unintended failure in the medication process, including the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional (HCP), patient or consumer, which leads to, or has the potential to lead to, harm to the patient. 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 and the Agency have a number of obligations as detailed in Title IX of Directive 2001/83/EC and Regulation (EC) 726/2004, chapter 3, Article 28. These relate to the recording, reporting and assessment of suspected adverse reactions (serious and non-serious) associated with an error in the prescribing, 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 between 4.5 and 21.8 billion €[1]. Individual studies have reported inpatient medication error rates of 4.8% to 5.3% and in another study, prescribing errors for inpatients occurred 12.3 times per 1000 patient admissions[2]. In in most cases medication errors are preventable, provided that the potential risks of medication errors have been considered during the product development and early marketing phases (when most medication errors will occur), 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 incorporated into a continuous quality improvement (CQI) program.

2. Scope

This guidance outlines the key principles of risk management planning in relation to medication errors arising from the medicinal product (such as those related to the design, presentation, labelling, naming, and packaging). This guidance describes the main sources and categories (types) of medication error which may need to be considered, uses real-life examples of such errors, the measures implemented to minimise the risk of these occurring and suggests proactive approaches to risk management planning throughout the product life cycle. The recording, coding, reporting and assessment of medication errors is covered in a separate guidance document.

[1] http://www.who.int/patientsafety/information_centre/reports/Alliance_Forward_Programme_2008.pdf
[2] Medication Errors: An Overview for Clinicians Wittich, Christopher M. et al. Mayo Clinic Proceedings , Volume 89 , Issue 8 , 1116 - 1125

3. Legal basis

Directive 2001/83/EC specifies that the definition of the term 'adverse reaction' should cover 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 error and any measures which may mitigate these risks. Commission Implementing Regulation 520/2012 defines the content and format of the risk management plan, with provision in Part II (the safety specification) Module SVI (Additional EU Requirements for the safety specification) for a discussion and description of medication errors which may be associated with the medicinal product.

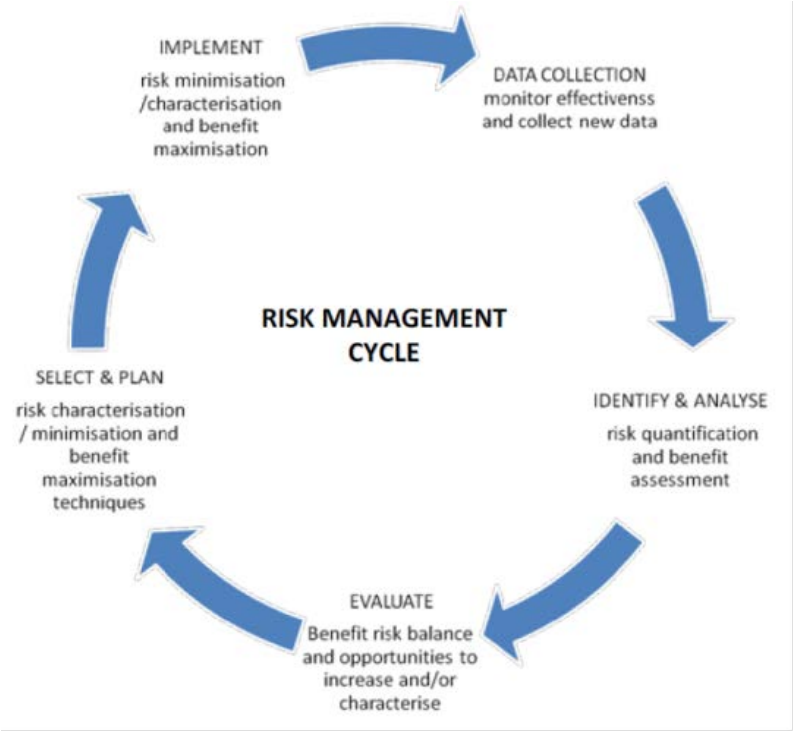
4. Definitions

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 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

Good Vigilance Practice Module V describes the general principles of risk management planning, which is a global process, continuous throughout the lifecycle 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.



It is vital that risk management planning in relation to medication errors is proactive and begins at a very early stage in product development. Medication errors can arise at any stage of treatment process, including prescribing, dispensing, preparation for administration, administration and provision of information. Such errors can lead to over- or under-dosing, incorrect application via the wrong route of administration or administration to the wrong patient population. The consequences may include 1) serious adverse reactions including death, 2) an increased incidence and/or severity of adverse reactions and 3) loss of efficacy.

During the product development process, Marketing Authorisation Holders (MAHs) 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. MAHs should consider whether any significance changes to the marketing authorisation may increase the risk of medication error. Such changes may include (but are not limited to) introduction of a product that differs from an authorised/established product regarding:

- concentration or strength
- pharmaceutical form
- composition
- method of preparation
- route of administration
- different administration device
- used in a different patient population or indication
- inbuilt distinguishing features in terms of appearance (e.g. design and appearance of insulin pen device).

The RMP should be used to document the safety considerations given to product design and should be kept updated during the product life-cycle, in a dedicated section which describes the potential for

medication errors (GVP V.B.8.6.4 module SVI). This includes a detailed description of medication errors which may occur based on the product design (including packaging), pharmaceutical properties and pharmacology of the product, and at all stages: dispensing, preparation for administration and administration. The RMP should also include aggregated data in the form of a summary of medication errors identified during the clinical trial programme (and any preventative measures taken as a result of these reports), the effects of device failure (where relevant) and a summary of any medication errors reported with the marketed product. Any risk minimisation measures proposed by the MAH to reduce confusion between old and new "product" (where significant changes to the MA or line extensions have been introduced) should be discussed in the RMP.

When a potential risk of medication error has been identified, medication error should be captured in the RMP as an important risk and both routine and additional risk minimisation measures may be in place in place to reduce the risk of medication error. Furthermore, MAHs have an obligation to describe and discuss patterns of medication errors and potential medication errors within every Periodic Safety Update Report (PSUR), even when these are not associated with adverse reactions. The context of product use, including the setting, stage of medication process, category (type) of medication error, contributing factor(s), medicinal product(s) involved, covariates defining the treated population, patient outcome, seriousness, mitigating factors and ameliorating factors should be considered and discussed in relation to these reports. These factors are relevant not only for root-cause analyses but also for developing appropriate risk minimisation measures.

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 what 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 what measures may mitigate the risk of medication errors occurring. Although some medication errors may occur at the treatment phase, many of these could 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 error[3].

5.2.1.1. Product design

Many different designs of medicinal product are available and all may be associated with medication error. The US Food and Drug Administration[4] has developed guidance on safety considerations for product design to minimise medication errors; this guidance is complimentary to EU guidance and may be useful to consider. A high-level overview of the most common sources of medication error based of the design of product is included in Annex 1.

Medication Errors in the context of the therapeutic armamentarium

It is important to explore the potential for medication errors in the context of the available therapeutic armamentarium and where a new product may sit within this. 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 with the same indications due to similarities in posology, appearance, method of administration, strength or packaging.

[3] 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)
[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm331808.htm

5.2.2. Typical errors during the clinical trial programme

Subjects in clinical trials are typically closely monitored and have at least semi-regular contact with study investigators during the trial. This controlled environment may therefore not reflect 'real world use', but even in the clinical trial scenario, medication errors may still occur. One study[5] of cancer clinical trials suggested the most common type of errors were prescribing (66%), improper dose (42%), and omission errors (9%). The study found that not following an institutional procedure or the protocol was the primary cause for these errors (39%), followed by the written order (30%), and poor communication involving both the healthcare team and the patient (26%).

Common sources of medication errors in trials may relate to use of small font sizes and absence of information on dose/strength in the plain packaging used for investigational products and such factors are unlikely to impact on the marketed product's design or presentation. However, the clinical trial setting may be particularly useful for identifying any difficulties using medicines presented with a device or as a premixed solution for administration. This may allow for an early indicator of refinements that may need to be made to the design of the product or instructions for use prior to labelling, approval and marketing.

During clinical trials, it may become evident that some drug product design features increase the risk of medication errors. In this scenario, Applicants should provide an appropriate risk analysis for medical errors detected in the clinical trial programme and use this as a basis for refinement in the proposed pharmacovigilance and risk minimisation activities (or both).

5.2.3. Data from "failure mode and effects analysis" and "human factor testing" (pre-authorisation)

Successful risk management is based, in part, on effective quality management systems and a number of tools may be useful in proactively identifying and assessing the risk of medication errors.

The FDA guidance on safety considerations for product design referred to in chapter 5.2.1.1. recommends two tools in particular, "failure mode and effects analysis" (FMEA) and "simulated use testing" (also known as "human factors" or "usability" or "user" testing). The report of the EMA's 2013 workshop on medication errors[6] notes the Pharmaceutical Industry's suggestion to use other methods of human factor engineering that test how the actual product is used, such as the "perception-cognition-action" (PCA) analysis, to be carried out early in development.

For medicinal products delivered via an administration device, the International Standard for usability testing for medical devices should also be followed (ISO/IEC 62366: Medical Devices – Application of Usability Engineering to Medical Devices[7]).

5.2.3.1. Failure mode and effects analysis (FMEA)

The Institute for Safe Medication Practices (ISMP) has issued guidance on the principles of conducting FMEA[8]. Broadly, this involves analysis of all the potential sources of 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.

[5] J Clin Oncol (Meeting Abstracts) June 2007 vol. 25 no. 18_suppl 6547
[6] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf
[7] http://www.iso.org/iso/catalogue_detail.htm?csnumber=38594
[8] https://www.ismp.org/tools/FMEA.asp

In addition to errors due to product design (Annex 1), failures may relate to the product name, labelling and marking with Braille, the presentation of packaging and issues relating to storage of medicines. FMEA should assess all of these factors.

5.2.3.2. Simulated use testing

There is currently no legal requirement for user-testing of instructions for use or administration or reconstitution of medicines in order to investigate the potential for medication errors.

Applicants who have performed simulated use testing are encouraged to provide the data as supporting evidence in EU applications. Applicants may also be asked to provide such data if there is concern over the risk of medication error during the assessment of the application.

5.2.4. Defects and device failure (pre-authorisation)

For medicinal products delivered via device, the International Standard (ISO 14971:2007 Medical devices - Application of risk management to medical devices[9]) should be followed. 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 re-usable or refillable (e.g. a syringe marketed pre-filled with a drug) are covered by medicines legislation. However, in addition to this, the relevant essential requirements in Annex 1 of the Medical Devices Directive 93/42/EEC[10] also apply with respect to safety and performance related features of the device (e.g. a syringe forming part of such a product).

Some of the medication errors related to medicines administered via devices are described in Annex 1 but these largely relate to errors which may occur even when the medicinal products are within quality standards or devices are functioning normally. 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 misuse the product. Further information on the distinction between a product quality issue and a medication error is included in the Good Practice Guide for the Recording, Coding, Reporting and Assessment of Medication Errors.

For medicinal products delivered via 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, non-functioning of inhaler devices under normal conditions of use or after dropping of the device (and other real-life examples encountered in the context of patient safety incident reporting described in Annex 1 and in the guidance on risk minimisation strategies for high strength and fixed combination insulin products included as an addendum to this guidance).

5.2.5. Medication errors resulting in harm during post-authorisation phase

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.

Prescribing

[9] http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_detail_ics.htm?csnumber=38193
[10] http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/medical-devices/

A prescription is a written order, which includes detailed instructions of what medicinal product should be given to whom, in what formulation and dose, by what 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 all such HCPs are aware of the errors that may be introduced at the prescription stage.

Prescribing errors may relate to stipulation of the wrong drug, dose, strength, indication, route of administration/pharmaceutical form or length of treatment. Medicinal products with a narrow therapeutic window or which are toxic in overdose may be particularly associated with medication errors if errors in dosing occur (e.g. a patient with chronic back pain developed respiratory failure after being prescribed oral morphine 100mg MST BD in instead of morphine 10mg MST BD).

Medicinal products may not be down-titrated appropriately; a patient developed 'grey man syndrome' when prescribed amiodarone 200mg three times daily for a month instead of being down-titrated to 200mg daily after a week. In some situations the periodicity of dosing may differ across various indications, e.g.:

- cases of methotrexate overdose have been reported in patients who took methotrexate once daily instead of once weekly for anti-inflammatory purposes and this has led to an update of the label to state that the medicine should be taken once weekly
- 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 and patients should be monitored for infusion-related ADRs.

It is important to consider situations when immediate-release and slow- or modified-release formulations are available and in this case the intended formulation should be clearly indicated on the prescription e.g.:

- 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 to highlight the once-daily dose regimen for the prolonged-release formulation.
- Incorrect dosing with pramipexole was reported when the immediate-release formulation was mistaken for the prolonged-release formulation and accidental overdose was reported when prolonged-release formulations were crushed for ease of swallowing. Packaging was redesigned to differentiate between the two products and packaging and Package Leaflet for the prolonged-release formulation carries a clear warning that the medicine must be swallowed whole and not chewed, divided or crushed.

Handwritten prescriptions may introduce errors through use of abbreviations, particularly when handwritten, (e.g., 'OD' can mean once daily or right eye, 'QD' (once daily) may be misread as 'QID' (4 times a day), 'U' (used as an abbreviation for 'units') may be read as zero, trailing zeroes may be used so that 1.0mg is read as 10mg). Hard-to-read handwriting, misspelling of drug names and lack of detail on dose and quantity may also introduce mistakes in prescriptions. The ISMP has previously published a call to action to eliminate handwritten prescriptions[11] and this focused on eliminating the

[11] https://www.ismp.org/Newsletters/acutecare/articles/Whitepaper.asp

use of error-prone abbreviations by healthcare professionals. The widespread use of electronic prescribing systems generally eliminates such errors. However, it is still possible to select the wrong drug, dose and quantity from drop-down menus for inclusion in electronically-produced prescriptions. It is also important that electronic systems can be designed or updated to capture all key areas of prescribing information, sufficient to minimise errors.

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 (e.g. a patient with chronic obstructive airways disease was reported to have collapsed and experienced breathing difficulties when we was prescribed prednisolone 40mg once daily for 7 days but was instead given propranolol 40mg once daily). Such errors may arise due to similarities in packaging design, strength not being clearly highlighted and similarities in product name. Where dispensing labels are used, further errors may be introduced by the dispensing label if these carry incorrect dosing instructions and there may be inconsistency between the dispensing label and the product supplied such as drug name, strength or pharmaceutical form.

It is also possible that a prescription may be dispensed to the wrong patient altogether, particularly in the hospital environment or care home. Good practice to avoid such errors could include asking a patient specifically if the product they have been dispensed is the one they usually get and checking that it is the product generally recommended in treatment guidelines.

It is common for patients to be given medicinal products when discharged from hospital and this may be another source of error (e.g. a patient who underwent percutaneous intervention was not given any antiplatelet medication aspirin or clopidogrel and discharge was rushed, meaning that medications given on discharge were not explained; this patient received no antiplatelet medications for 2 weeks and was readmitted with blocked stents).

Preparation and administration

Some medicinal products for IV use or parenteral administration require preparation, dilution or reconstitution prior to use and this may introduce medication errors, examples of which are illustrated below:

- lack of efficacy was reported with leuprorelin suspension for injection due to errors in the preparation, mixing and administration of the product, requiring amendment of the instructions for use/reconstitution.
- there have been numerous reports of medication error (some fatal) when concentrated solutions of potassium chloride have been given to patients without first being diluted or if erroneously substituted for sodium chloride. This has led many national safety organisations to issue recommendations on the stocking, storage, handling and labelling of concentrations potassium chloride to minimise these risks.
- 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, a leaflet and product information describe the correct dilution for administration by subcutaneous (SC)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 as two ampoules (one containing water as the solution for injection and another containing the powder for solution) was labelled only with the trade name. This introduced the possibility for misunderstanding, because the ampoule with the solution may be mistaken for the medicinal product containing the active substance and the patients may receive only water for injections. The product was relabelled to make it clear that the ampoule containing a solution contained water for injection, for use with the active substance. Treatments given by the intravenous (IV) route are associated with the highest rates of preparation and administration error due to issues such as incompatibility with diluents or by injecting bolus doses faster than the recommended slower infusion time. Medicinal products for IV use may be inadvertently given by the subcutaneous (SC), intradermal or intra-muscular (IM) route rather than by infusion. Cases of needle contamination can also result in accidental exposure to product or exposure to contaminated device (e.g. a case of adhesive arachnoiditis and paraplegia was reported when chlorhexidine, used as topical disinfectant in epidural or spinal anaesthesia procedures reached the meninges via a contaminated spinal/epidural needle).

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.

Where medicinal products are self-administered by patients, the underlying reasons for medication error or accidental overdose may include lack of understanding of the dose regime. Risk factors for medication errors include decline in patients' renal or hepatic function (both associated with higher medication error rates), patients' impaired cognition, comorbidities, dependent living situation, non-adherence to medications, and polypharmacy. Advanced age is also a patient-related risk factor for medication errors.

Errors of omission (where the drug is not administered to the patient) may occur for a variety of reasons. Such errors can be critical if control of a medical condition requires regular medication (e.g. a patient with epilepsy was hospitalised with seizures when they ran out of supplies of carbamazepine and could not get a repeat or emergency supply). Other sources of errors of omission may include failure of communication between staff, especially when transferring patients between different units or hospitals, or failure to keep accurate drug administration records.

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 monitored and 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. Product information should include clear instructions on the most appropriate dosing time (if this is important) and whether the medicines can or should be taken with food and drink. There may also be use of medicinal products in patients who have allergies to such treatment; product information for all medicinal products should carry a contraindication for use in patients with known hypersensitivity to the active substance or excipients.

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 a guidance document included as an addendum to this guidance.

Device failure

Device failure can occur in the post-marketing setting, e.g.:

- misplacement of dexamethasone 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 prefilled 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 number of other examples of device-related medication errors are included in Annex 1. Where such failures 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 for the Recording, Coding, Reporting and Assessment of Medication Errors.

5.2.5.1. Reporting and Coding of medication errors

Guidance on the reporting and coding of medication errors is provided in the Good Practice Guide for the Recording, Coding, Reporting and Assessment of Medication Errors.

5.2.5.2. Root cause analysis

The root cause analysis (RCA) is a structured method used to analyse serious adverse events derived from 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).

A multidisciplinary team should analyse the sequence of events leading to the error. RCA should be performed at local level in order to prevent future harm by eliminating the latent errors and to ensure confidentiality.

A RCA should be conducted for any medication errors detected in the post-marketing environment so that lessons can be learned from serious incidents which may in turn reduce the likelihood of future incidents. The PSUR and RMP can both be used to document and analyse reports of medication error related to the design, presentation, labelling or naming of the medicinal product and where the need for risk minimisation measure and or communication can be taken..

A RCA has 3 basic steps:

1. Identification of the problem (including details of what happened, when, where and in what situation, and what the impact of the event is on stakeholders)
2. Identification of causes of the problem (describe the processes that led to the problem and identify the stages at which error could have or did occur)
3. Identification of solutions (identify possible or potential solutions from sources of error in the process)

6. Measurement of success of measures taken

6.1. Risk minimisation measures

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

This guidance is complimentary to the recommendations in Good Vigilance Practice Modules V[12] (Risk management) and XVI[13] (Risk minimisation measures: selection of tools and effectiveness) which offer guidance on the development of risk minimisation tools.

Routine risk minimisation

Routine risk minimisation measures apply to all products and include:

- the summary of product characteristics;
- the labelling;
- the package leaflet;
- the pack size(s);
- the legal status of the product.

Pack size limitations can reduce the risk of medication errors in the form of patients taking too many tablets (leading to overdose) and require the patient to return to the prescriber, who can check the status and progress of the patient and that the medicine is being used correctly.

It is important to consider whether critical information to avoid medication errors included in documents such as the SmPC and Patient Information Leaflet is likely to be read by HCPs, patients or care givers or whether more prominent warnings should be included on the packaging so that these are not overlooked (e.g. the labels for generic piperacillin/tazobactam carry a statement that they must not be mixed or co-administered with any aminoglycoside, and must not be reconstituted or diluted with lactated Ringer's (Hartmann's) solution; a similar warning is not required for the branded product as this has been reformulated to remove these incompatibilities).

Additional risk minimisation

Additional risk minimisation measures may also be necessary in some circumstances and these encompass any measures beyond labelling, pack size and legal status. Additional risk minimisation measures should focus on the prevention of medication errors, but the burden of imposing such measures on patients, HCPs and the healthcare system should be balanced against the benefits.

The most common form of additional risk minimisation is educational materials for HCPs and patients, but other approaches may also be considered in agreement with National Competent Authorities (e.g. educational videos showing correct reconstitution and injection of a solution, prescriber's checklists to ensure that appropriate pre-treatment tests have been performed, demo-kits for complex devices). Educational materials are predominantly paper-based but as risk minimisation evolves it is likely that MAHs will consider supplementing such materials with by internet-based activities and new technologies in prescribing and dispensing systems to improve safe medication practice, such as smart phone apps, bar–coding and pill identifier websites. This should be discussed and agreed with national competent authorities in all cases with input sought from the Working Group on Quality Review of Documents as necessary.

[12] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf
[13] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf

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 to monitor their effectiveness.

6.1.1. Error prevention at product design stage

A number of common sources of medication error which should be considered at the product design stage are described in Annex 1 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 and who will use it and conduct a suitable analysis of potential medication errors (see section 2.2.3). From these, the MAH should consider what risk minimisation may be introduced in the design of the product to reduce the risk of medication errors; a number of suggestions are included in Annex 2.

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

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

6.1.2.1. Naming

International Non-proprietary Name (INN)

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

- INN should be distinctive in sound and spelling. They should not be inconveniently long and not be liable to confusion with names in common use.
- Use of common 'stems' for products which are in related pharmaceutical classes (e.g. -azepam for diazepam derivatives, -bactam for beta-lactamase inhibitors, gli- for sulfonamide hypoglycaemics).
- To avoid confusion neither trade-marks nor product brand names should be derived from INNs nor contain common stems used in INNs.
- It is important to note that the alternating use of brand names and INNs may lead to inadvertent overdosing, should patients be treated with multiple products containing the same active substance.

However, it is also important to consider the potential for confusion between products due to similarities in the INN. These 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. flucloxacillin recorded in place of the prescribed fluvoxamine, prochlorperazine prepared instead of promethazine). The FDA and ISMP recommend the use of Tall Man letters where part of the INN or drug name is written in upper case, to help distinguish sound-alike and look-alike INN or drug names from one another, making them less prone to mix-ups (e.g. NovoLOG and NovoLIN and HumaLOG and HumuLIN[14]).

[14] http://www.ismp.org/tools/confuseddrugnames.pdf

Brand Name

The CHMP has issued guidance on the acceptability of names for human medicinal products processed through the centralised procedure[15]. This includes that the name should not convey a promotional message, have 'bad' connotations in any of the official languages, be misleading in therapeutic, pharmaceutical or composition terms or cause confusion in print with any other branded product or established INN. The MAH should take this guidance into account when proposing invented names to the competent authorities.

There have been some examples of brand name mix-ups or errors, e.g.:

- In Italy, Diamox (acetazolamide) has been mistaken for Zimox (amoxicillina triidrato)
- In Ireland, confusion arose between the brand names Lasix (frusemide) 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 trade names Faustan (active substance diazepam) and Favistan (active substance thiamazole) and consequently the MAH changed the 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.

For centrally authorised medicines, the potential for medication errors arising from the name of the medicinal product is assessed (for centrally authorised medicinal products) by the EMA's Name Review Group, who have issued guidance on this matter[16]. The Group reviews the proposed (invented) name of medicinal products and considers whether invented names may convey misleading therapeutic or pharmaceutical connotations, be misleading with respect to product composition of the product, be promotional, cause confusion in identifying medicinal products, or create difficulties in pronunciation (or have any inappropriate connotations) in the different EU official languages.

6.1.2.2. Labelling and livery

The aim of good labelling is: correct description of the medicine, clear product selection and identification, information ensuring safe storage, selection, preparation, dispensing, and administration as well as track and trace. The design of labelling and packaging may lead to mis-selection of medicinal products, therefore all medicinal products placed on the market are required by Community law to be accompanied by labelling and package leaflet which provide a set of comprehensible information enabling the use safely and appropriate. 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 the medicinal product, dosage unit, pharmaceutical form, list of excipients, method/rout 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, information on Braille. On the printed outer packaging material, an empty space should be provided for attaching the prescribed dose. The use of the Quality review of Documents (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 guideline[17] provides guidance to ensure that the information

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

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

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

presented is accessible and understandable. In addition, several organisations have published design for safety guidances (NHS). The special space constraints on small containers (vial) and blister packs should also be taken into consideration.

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 healthcare professionals and patients and it is therefore important to assess such livery to determine whether it may give rise to a risk of medication error. Package design and livery should not compromise other distinguishing features of the medicinal product e.g.:

- 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 packaging livery 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 unvaccinated children did not receive the appropriate booster immunisation against diphtheria, tetanus and poliomyelitis with Revaxis. The MAH amended the packaging for Repevax to help distinguish it more clearly from Revaxis and this change was also communicated to HCPs.

If a MAH markets two or more products in the same therapeutic area which have a similar company livery, the possibility of mix-ups between the medicinal products must be considered (and labelling amended accordingly). This issue has been identified for injectable insulin products;

- a patient developed hypoglycaemia after being prescribed Insulin Novorapid 16 units twice daily instead of Novomix
- the presentation of different insulins in the same Flexpen device has led to reports of mix-up between these two insulins.

Clear distinction between medicinal products may be achieved by use of different colours, 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 have issued guidance[18] 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.

The guidance highlights the problems which may arise from these, including a limited variety of available colours and lack of common understanding of colour coding conventions.

Specific risk minimisation strategies e.g. for high strength and fixed combination insulin products administered in pre-filled pens are provided in a guidance document included as an addendum to this guidance.

[18] http://www.ismp.org/newsletters/acutecare/articles/20031113.asp

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 available in different strengths, and where the risk of under- or over-dose is potentially severe, it may be necessary to highlight the strength 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, 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.

Different manufacturers 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 (although there are isolated examples; in the UK there is a colour-coding convention for warfarin tablets wherein 0.5 mg tablets are white, 1 mg tablets are brown, 3 mg tablets are blue and 5 mg tablets are pink). However, choice of colour should be considered in product design (e.g. pharmacists have raised concerns that a fixed-dose combination of vilanterol and fluticasone furoate with indications in the maintenance treatment of asthma and 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).

6.1.2.3. Use of illustrations and pictures in product information

Product information often includes illustrations on use of the product or reconstitution prior to use. The MAH 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 2.2.3, 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 and 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 QRD recommendations on pack design and labelling for centralised non-prescription products[19] summarises basic principles.

[19] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/04/WC500104662.pdf

6.1.3. Risk minimisation tools and activities

6.1.3.1. For patients/caregivers

Key to risk minimisation and prevention of medication errors is the provision of a suitable PL which describes the correct use of the medicinal product. There is a requirement to include a user-tested PL 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, National Competent Authorities may publish guidance on their websites on practices to reduce the risk of medication error (e.g. the Medicines and Healthcare products Regulatory Agency 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 patients[20]).

Participants in the EMA workshop on medication errors (2013) suggested a number of activities to mitigate the risk of medication error, which are not part of any formal guidance. These include the use of separate medicine cabinets for different household members and the use of more sophisticated tools that can help to prevent medication errors (e.g. smart phone applications which remind patients to take their medications on time and track medications which have been taken, and websites which carry pill identifier tools to help patients identify medicines).

6.1.3.2. For Healthcare professionals

HCPs are responsible for ensuring that patients are prescribed and receive the appropriate medication without errors. Where patients are responsible for the administration of the medication themselves, HCPs should ensure that the patient understands how to self-administer the medications appropriately in order to minimise the risk of medication errors.

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. The use of pop-up reminders in e-prescribing systems may be useful in reminding the prescriber to specify details of the prescription, e.g. strength of insulin. Other tools which may assist HCPs in prescribing appropriately may include the use of reminder cards (e.g. the healthcare professional's reminder card for vismodegib, which is teratogenic, contains information for men and women on the importance of adequate contraception and pregnancy testing), reminder posters and prescriber guides and checklists.

Pharmacists

Pharmacists may play an important role in verifying that the treatment is appropriate for the patient and identifying potential prescribing errors before the medication is dispensed to the patient. The pharmacist may identify issues by speaking to the patient or by consulting dispensing records. Although it is important to be discreet and not to undermine the confidence of the patients in the prescriber, the pharmacist is well-placed to ask such questions as whether the patient has received the medicine before. If any aspect of the prescription appears to be inappropriate for the patient (e.g. it is contraindicated, dosage appears to be excessive, or if a medicine requires a negative pregnancy test

[20] http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266132

before being dispensed) this can usually be verified by contacting the prescribers whose details are included on the prescription.

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.

The following list of common dispensing errors identified in hospital Pharmacies[21] highlights the importance of checking that details of each prescription have been transcribed correctly and medicinal products selected carefully in order to minimise the risk of medication error, including:

- *Dispensing medicinal product for the wrong patient (or for the wrong ward)*
- *Dispensing the wrong medicinal product*
- *Dispensing the wrong drug strength*
- *Dispensing at the wrong time*
- *Dispensing the wrong quantity*
- *Dispensing the wrong dosage form*
- *Dispensing an expired or almost expired medicinal product*
- *Omission (i.e. failure to dispense)*
- *Dispensing a medicinal product of inferior quality (pharmaceutical companies)*
- *Dispensing an incorrectly compounded medicinal product (compounding in pharmacy)*
- *Dispensing with the wrong information on the label:*
    - *Incorrect patient name*
    - *Incorrect medicinal product name*
    - *Incorrect strength*
    - *Incorrect instruction (including incorrect dosage)*
    - *Incorrect medicinal product quantity*
    - *Incorrect dosage form*
    - *Incorrect expiry date*
    - *Omission of additional warning(s)*
    - *Incorrect pharmacy address*
    - *Other labelling errors*
- *Dispensing with the wrong verbal information to the patient or representative*

For some of these errors, the risk may be increased for some medications. These include medications with similar names (INN or brand name) or similar packaging, medicinal products which are available in multiple strengths and or formulations, including different delivery devices, and situations where the same active ingredient is present in different medicinal products for different indications.

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

6.1.4. New technologies

A study of the prevalence and causes of prescribing errors in general practice in England[22] suggested that prescribing or monitoring errors were detected for one in eight patients. The most common types of prescribing error were “incomplete information” (37.9%) ‘‘unnecessary drug’’ (23.5%), ‘‘dose/strength error’’ (14.4%) and ‘‘omission’’ (11.8%). The study recommended GP training, continuing professional development, clinical governance, the effective use of clinical computers, and improving systems to support safe medicines management.

In recent years there has already been increased use of technology in prescribing and dispensing systems. Such new technologies go beyond the regulatory tools for mitigating the risk of medication error (which are the responsibility of national competent authorities and MAHs) but they may provide a valuable contribution to minimising the risk of medication errors. The inclusion of the following in this guidance in intended only to raise awareness of those tools, including:

- Use of prescribing software for general practitioners including prescribing decision support software which can check the correct medicinal product and dosage form, correct dose calculations, cross-check information on allergies, provide information on known drug interactions and adjustment of dosages in patients with renal or hepatic dysfunction;
- Electronic prescribing services (EPS) where prescriptions are sent electronically to a dispenser (such as a pharmacy) of the patient's choice
- Automated medicine-dispensing robots and automated dispensing cabinets in hospitals, which can reduce dispensing errors by packaging, dispensing, and recognizing medicinal products using bar codes
- Use of bar-coded medication administration (BCMA) systems in hospitals to check and record that the right patients has received the right medicinal product at the right time; such systems can be expensive to implement and maintain but were shown to reduce the medication error rate in an intensive care unit by 56%
- Use of electronic health record (EHR) to ensure that all relevant information is taken into consideration at prescription and during administration.

6.1.5. 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.

Collaboration 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 but for medication errors associated with ADR 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

[22] http://www.gmc-uk.org/Investigating_the_prevalence_and_causes_of_prescribing_errors_in_general_practice___The_PRACtICe_study_Report_May_2012_48605085.pdf

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 for the Recording, Coding, Reporting and Assessment of Medication Errors.

Routine pharmacovigilance through monitoring of spontaneous reporting systems is the most commonly-employed method of measuring the success of risk minimisation activities but it has major limitations and alternative proposals should be made wherever possible.

A Post-Authorisation safety Study (PASS) can be a useful method to show how patterns of use or reporting of errors may have changed before and after safety communications or changes in product labelling, and may also identify sources of medication in the post-approval setting, e.g.:

- 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 spontaneous reporting showed cases were still being reported with no clear trends of improvement observed after the issuance of the DHPC. The MAH was asked to implement further risk minimisation measures to manage the risk of medication error through overdose including updates to product information and educational material for prescribers. The MAH was required to measure the success of these measures through additional Pharmacovigilance in the form of a DUS.

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, e.g.

- 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 is underway to 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.

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, 'Risk minimisation measures: selection of tools and effectiveness indicators'[23]; Guidance on the key elements of survey methodology is included as an Appendix to GVP Module XVI.

[23] 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

Paediatric patients may be at particularly high risk of medication errors due to their variation in age, size and weight, body surface area (BSA) and degree of development. This is reflected in the dosing instructions for some paediatric products which express dosage and strength by bodyweight rather than by age in months or years.

Overdose was the most commonly reported medication error (accounting for 21% of all reports) in a study of paediatric patients (Manias et al 201324) while underdosing in certain paediatric specialties was the most commonly reported medication error in these settings (Bolt et al 2014[25]). 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 recalculation of drug doses is required. Due to the need to find the right dose based on weight (or BSA) for the majority of paediatric medicines, mathematical miscalculations may be more likely in paediatric patients than adults.

Occasionally there is a need for complex dilutions by medics/nurses/pharmacists; medication errors with infusion of fluids and electrolytes are common. For liquid oral medications there is some evidence that oral syringes may be the most accurate dosing device[26]. However, liquid formulations may present a risk of medication error if the wrong dosing device is used to deliver them (e.g. a liquid oral formulation of paracetamol was presented with a dropper graduated in mL for infants less than 3 years and an oral syringe graduated in mL for infants older than 3 years; use of the oral syringe in infants could lead to a risk of overdose).

Historically there has been a lack of development of paediatric medicines and lack of clear guidance on paediatric dosing in product information or other sources, leading to off-label use of medicinal products with indications in adult populations. The situation has improved with the introduction of the paediatric regulation in 2006 (Regulation (EC) No 1901/2006) that places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. However, the ongoing limited availability of paediatric formulations may lead to misuse of product formulated for adults.

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

Apart from neonates, the risk of medication errors in paediatric patients may also be increased in circumstances where high risk medicines, specific drug combinations and formulations are used, or

[24] 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
[25] Bolt R et al, Journal of Clinical Pharmacy and Therapeutics, 2014, 39, 78–83
[26] 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

where untrained healthcare workers are involved, and in transitions of care such as admission and discharge. Paediatric patients with chronic conditions and/or complex medication regimes (e.g. children with learning difficulties, oncology patients) may also be at particular risk of medication error due to the added complexities of dosing or polypharmacy in these patients.

Consideration should also be given to the prevention of accidental ingestion 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 in practice the use of locked containers or medicine cabinets which cannot be reached by children should be encouraged.

6.2.2. Elderly patients

The elderly account for 34% of all written prescriptions and are at high risk of medication errors. Elderly patients frequently use multiple medicinal products (polypharmacy) and this can lead to mix-ups and other administration errors. Elderly patients may also have difficulty swallowing, particularly in diseases such as stroke or Parkinson's disease. This can lead to accidental underdosing, which should be managed appropriately by use of formulations which are easier for such patients to swallow. Other problems which are common in elderly patients and which may increase the risk of medication error include insufficient intake of fluids. There may also be excessive use of over-the-counter (OTC) products, e.g. laxatives or herbal medicinal products, which doctors are likely to be unaware of but pharmacists may be better able establish. Older patients with diabetes may be more likely to have impaired eye sight than younger patients which may have implications for the correct use of insulin pens.

Elderly patients, particularly those in shared living environments with caregivers who have responsibility for several patients, may be vulnerable to mix-ups with other patients' medications. Older patients with manual dexterity issues may also have difficulties opening containers or blisters or in handling medical devices and this should be taken into consideration in product design for medicinal products intended for diseases of old age.

It is important the 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 not to rely solely on the provision of information via the internet, as elderly patients are less likely to make use of such materials than younger patients. For (very) elderly patients, the internet is the least preferred option for provision of educational materials to ensure correct use of a medicinal product. For this age group, the caregiver, nurse and family should 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 or low literacy

GVP Module V (Risk Management Systems) 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. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment. Patients with low literacy are likely to have difficulty following and understanding instructions for use. This may be a sensitive issue to discuss with patients or their carers and underlines the importance of patients being fully counselled on the use of their medicine by HCPs in preference to being left to educate themselves using printed materials.

6.3. Communication

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

For communication of safety information in product information, the CHMP has issued guidance on the readability of the labelling and package leaflet of medicinal products for human use[27]. The standard content and format of the PL is defined in Directive 2001/83/EC and it should be written in simple language, understandable by the layperson. The PL must be up-to-date and 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 listed adverse reactions side-effects should be assigned an appropriate frequency category. The use of the term "unknown" or "not known" in relation to frequencies of ADRs should be avoided whenever possible in the PL as this is not helpful to patients in helping them to understand the degree of risk, and may even raise alarm). It would be better to use language such as "Other side effects which may occur include…" or "Although it is not know exactly how often it occurs…" (or similar) in situations where no frequency has been designated for a given ADR.

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 Group[28] 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 PL 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 PL 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, but these documents can be lengthy and they are not always consulted. When the risk for Medication error has been identified 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 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 RMPs.

At a European level, the SCOPE project has a dedicated work package[29] 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

[27] http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf
[28] Creation of a better medication safety culture in Europe: Building up safe medication practices', Council of Europe Expert Group on Safe Medication Practices (2006)
[29] http://www.scopejointaction.eu/work-packages/wp6-risk-communications/

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 (ICRSs).

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 error and intercepted errors (or near misses) is provided in the Good Practice Guide for the Recording, Coding, Reporting and Assessment of Medication Errors.

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 healthcare professionals and patients. For this purpose EU 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 healthcare professionals 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 the reporting from patients, including clarity about what to report and how, including a feedback mechanism to encourage further engagement.

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 the obligation to evaluate the information held in their pharmacovigilance system scientifically, to detect any change to a medicine's risk-benefit 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.

7.2. Pharmacovigilance Risk Assessment Committee (PRAC)

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 and the coordination group 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 EMA workshop on medication errors called for pro-active engagement and capacity building with patient consumer groups and healthcare professionals on a systematic basis to improve safe medication practices. To ensure risk minimisation measures tailored to prevent or minimise medication errors are effective in practice, patients, healthcare professionals but also caregivers and other healthcare providers depending on the healthcare delivery system where the medicinal product is intended to be used, should be included systematically in the design, user testing and communication strategy of risk minimisation measures.

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 risk management plan 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.B.8.6.4 risk management plan Part II, Module SVI.4 “Potential for medication errors” should include a stand-alone summary of aggregated data on medication errors which occurred during the clinical trial programme and/or post-marketing period.

For this purpose it is paramount 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) and 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 on this issue is provided in the good practice guide on the coding and reporting of medication errors.

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 European Medicines 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 EV database to determine whether there are new risks or whether the risk have changed and whether those risks impact on the B/R 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 B/R balance.

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

Annex 1 – Sources of medication error in medicinal product design

Tablets

- A large number of medicinal products are presented in tablet form, which can be associated with several sources of error. Patients may take the wrong dose in situations where multiple tablet strengths are available but presented in similar packaging and have a very similar appearance in terms of colour, size and shape. Similar problems may occur when a product is available in immediate-release and extended-release formulations but where the packaging and tablet appearance are very similar. Some medicinal products require a loading dose to be used initially and later replaced by a lower maintenance dose and adverse events may occur if this down-titration of dose does not occur. Similarly, up-titration may be required with a lower dose used for the first few weeks later replaced by a higher maintenance dose (e.g. initiation packs of retigabine are used for 2 weeks to deliver the initiation dose of 100 mg, three times daily (a total of 300 mg a day) which is gradually adjusted over the following weeks up to a maximum dose of up to 400 mg three times daily (a total of 1,200 mg a day).
- 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. Other tablets may not be suitable for breaking (such as those with an enteric coating) but may be broken or cut and used by patients anyway.
- The size of tablet may make the medicinal product difficult to swallow for some patients and other tablets can be irritating to the oesophagus.
- Tablets are usually presented within foil-sealed blisters or within foil pouches but brittle or fragile tablets may break if pushed through foil too hard, which 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 also be difficult to open for patients with dexterity problems with the potential risk of injury from use of scissors or sharp objects to open the blister packs. Some formulations are developed for oral administration but should not be swallowed, including sub-lingual tablets, buccal tablets, melts and oro-dispersible tablets. These dissolve in the mouth, under the tongue or inside the cheek (e.g. asenapine sublingual tablets are placed under the tongue and allowed to dissolve; eating and drinking should be avoided for 10 minutes after administration) 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 effervescent formulations which must be dissolved in water before use but these could be crushed instead of dissolved and attempts may be made to dissolve (unsuccessfully) in liquids other than water.

Capsules

- Medicinal products are commonly presented in capsule formulations. Capsule shells are often made of gelatine which can become brittle if exposed to the 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 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 with the contents of the capsules inhaled through a device; such products may inadvertently be swallowed by patients.

Oral solutions and suspensions

- 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 and potentially less desirable than a graduated syringe. Liquid formulations are also likely to be presented with child-resistant-closures to reduce the risk of children accidently ingesting the medicine within but these can be difficult to open for patients with manual dexterity problems.

- Suspensions require shaking to produce homogenous solution 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 (e.g. fentanyl 'lollies'). Similarly, medicated chewing gum (e.g. nicotine replacement therapy) may be mistaken for regular chewing gum which could expose users (and especially children) to potential harmful doses of nicotine.

Patches

- The use of medicated patches has increased in recent years but these too may be associated with medication errors. 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 (e.g. as occurred with rivastigmine patches, reported in June 2010)

- Patches which are still pharmaceutically active may become accidentally stuck to other people (who are then exposed in error). This has occurred with fentanyl patches where in the US, up to April 2012 thirty cases of paediatric accidental exposure were identified , with children coming into contact with patches that were loosely attached to or had fallen off of the intended wearer, or that were stored or disposed of improperly; 10 of these cases resulted in death. There have also been instances where discarded patches have been thrown away and eaten by children.

- Patches may be adhered to non-recommended sites which may expose users to a higher dose than intended and cutting the patch into several pieces for ease of application may reduce the dose and efficacy or may cause the patch not to work at all.

- There have also been reports of patches containing metal as part of the adhesive backing causing skin burns when worn during MRI scans.

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.

Implants

- Some products are implanted into the body (e.g. contraceptive implants for insulin infusion pumps) and there may be errors associated with the insertion of the device or its removal, insertion in the wrong place(e.g. dexamethasone eye implant misplacement), devices moving or breaking internally (and perforating tissues), or becoming difficult to locate.

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Topical products

- Topically-applied medicinal products may include those intended for use on the skin or in the eyes or for rectal or vaginal use via an applicator and the design of the container (or applicator, or both) is important to ensure these can be applied safely and at the correct dose. Eye drops are often presented in a bottle or individual single-use droppers but these can be difficult to hold and use for patients with manual dexterity problems. Related to this, single-use droppers which are broken open to use may leave sharp edges which could damage the cornea (e.g. as with timolol and dorzolamide eye drops after the introduction of a new design of dropper, reported in July 2013). For drops presented in larger bottles, instructions for use vary and patients may squeeze the bottle excessively and deliver an overdose, which could have serious consequences particularly if administered at a too-high dose for a prolonged period.

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, meaning that a full dose may not be inhaled and the medicinal product may be largely deposited in the mouth instead. By contrast, breath-actuated dry powder inhalers (DPI) do not require careful timing of actuation and inspiration. However, since DPI rely on inspiratory airflow, these may be more difficult to use and be less efficacious for patients with poor respiratory airflow.

- There are a broad range of inhaler devices available and all differ in their design and function with 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 multiple dose-unit DPIs, the medicinal product inside must be regularly replaced. Inhalers may stop working altogether if dropped accidentally and where devices do not have a dose counter available it can be difficult to tell when the inhaler is empty.

- 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.

- Medicinal products given 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.

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 requires 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% Dextrose Injection USP, 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 the contents are not entirely mixed. There may be confusion over appropriate dosing when products are provided as concentrations, with difficulties calculating the correct dose in mg/ml or ml/kg for solutions presented as a w/v% concentration.

Presentation of the medicinal products

- The closure system for containers may be a source of error if solutions intend for topical or oral use are presented in same way and mistaken for products for injection. Some medicinal products are presented in a ready to use syringe but the potential for errors can arise if multiple strengths of a product are presented in a syringe with an identical fill volume.

Examples of medication errors involving Devices

- Patient received a 100 x overdose and died as a result of an insulin product being measured and administered using a 2ml intravenous syringe instead of a insulin syringe.
- Patient received a 5ml dose of oral antibiotic syrup intravenously as a result of the dose being measured and administered using a 5ml intravenous syringe instead of an oral/enteral syringe.
- Patient received a subcutaneous injection of adrenaline into the thumb rather than into the required site of administration due to confusion over how to operate a prefilled syringe device.
- A patient did not receive their required palliative care analgesic subcutaneous infusion for 6 hours, as a result of the nurse not correctly operating the syringe driver and setting a rate of infusion of 0ml over 12 hours.
- A paediatric patient received an overdose of infusion fluid as a result of an adult intravenous administration set being used instead of a paediatric administration set being used, where 20 drops = 1ml instead of 60 drops =1ml and the wrong rate of administration was set by gravity infusion.
- A patient became hypoglycaemic and died as a result of receiving treatment for hypercalcaemia when an insulin infusion was administered by syringe driver, and the glucose 10% infusion that should have been administered at the same time was turned off by accident.
- An overdose of vasopressor infusion occurred as a result of the volumetric infusion pump being mis-programmed at 100ml/hour instead of 10ml/hour.
- A 30ml syringe was used in a syringe driver pump instead of a 50ml syringe resulting in a overdose of a vasodilator infusion.
- The patient blood pressure failed to be controlled adequately as a result of a normal intravenous administration set being used in the volumetric infusion pump instead of a low adsorption set recommended by the manufacture.
- A patient experienced severe phlebitis as a result of the intravenous antifungal infusion not being administered via a filter, as recommend by the manufacturer.
- A patient with obstructive airways disease being treated with nebulised beta agonists went into respiratory failure as a result of the nebuliser device used to administer his therapy being powered by oxygen gas rather than medical air.
- A patient with obstructive airways disease being treated with oxygen therapy went into respiratory failure because a venture mask delivering the wrong percentage of oxygen was used.

Annex 2 – Design features which should be considered to reduce the risk of medication error

Tablets

- Tablets should differ in size, shape and/or colour and have clear markings if they are of different strengths, or are available in immediate- and modified-release formulations, or are different generic formulations of a particular substance
- Colour conventions should be followed where these have been agreed for a class or group of medicinal products (e.g. colour coding in the UK for different strengths of warfarin tablets, applicable to all manufacturers)

Figure 1: different strengths of warfarin

- Any score-lines for ease of breaking should result in a clean break and tablets that should not be broken or crushed should not be scored or an easy shape to break; equally, tablets that can be chewed or crushed without affecting efficacy or causing harm to the patient should be clearly labelled as such
- Tablets which are irritating to the oesophagus should be accompanied by clear instructions for use on avoiding harm (e.g. take with a full glass of water and patient instructed not to lie down after taking (e.g. alendronate))
- tablets which have proven difficult to swallow due to size or coating should be reformulated where possible
- Tablets/capsules presented in blister packs or in foil should be reformulated where possible to make them less friable and prone to breaking; if this is not possible, clear instructions for handling of the tablets (e.g. instructions not to push the tablets/capsules through the foil, or to peel back foil covering and remove the tablet from the blister) should be included and blister packs should be designed so that they are easy to open

Capsules

- Most capsule shells are made of gelatin but other materials (e.g. hypromellose) are available and may be more suitable than gelatin, particularly if they encapsulate particularly hygroscopic substances
- Labelling should highlight the importance of not exposing capsules to air until they are administered and not opening capsules before use (unless this is an approved way to use the medicine, e.g. sprinkling on food)
- Respiratory medicinal products presented in capsule form should carry clear instructions on using the capsule with the 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 clear instructions that the product is now intended to be swallowed and for how long the medicinal product should be left in place
- Medicinal products which may be mistaken for sweets should be packaged very plainly and should carry instructions to keep in a locked container out of reach of children
- Effervescent formulations should carry clear labelling on what fluids they can be dissolved in and how long they should be left to dissolve before taking

Patches

- Patches should carry clear labelling on where they should be applied, how long they should be applied for, whether they can be cut into smaller sizes and clear instructions on the proper and safe disposal of the patches (e.g. they should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded)
- Patches should be a visible colour or patterned (i.e. not skin-coloured or clear) so they can be clearly seen on the skin and are highly visible if they become detached and drop onto the floor. This is particularly important for products which are particularly dangerous in overdose (e.g. fentanyl patches)
- If patches contain metal foil or parts, this should be clearly indicated in labelling along with a warning that such patches should be removed in case of a MRI scan

Suppositories, pessaries and implants

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

Solutions, suspensions and topically-applied liquids

- Liquid medicinal products (especially for children) should be supplied 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 or spoon. Oral liquid medicinal products with a narrow therapeutic index should preferably be provided with a dosing syringe.
- Liquid medicines for patients with manual dexterity problems (e.g. rheumatoid arthritis) should be presented in containers with medigrip lids or if child-resistant closures (CRC) are necessary, CRCs with keys (which still allow ease of opening)
- Single-use eye droppers should be designed in such a way that there are no sharp edges after opening
- Bottles containing eye drops should be accompanied by clear instructions (including diagrams) on how to administer the drops and the importance of not squeezing the bottle if this is not how the drops should be dispensed from the bottle

Aerosols and inhaled medicinal products

- Clear instructions for use of inhalers (including diagrams) should be included in product information and along with a reminder that patients should be shown how to use the device and that their inhaler technique should be checked regularly
- Inhaled steroid medicines should be accompanied by a recommendation to rinse out the mouth after use to reduce the risk of oral candidiasis
- MAHs intending to market medicinal products presented as a pMDI should ensure that data on use with an appropriate spacer device is collected and seek authorisation in conjunction with a spacer device; and product information should include advice on spacers where this is approved as part of the SmPC
- Inhalers with removable dust caps over the mouthpiece should include a reminder in the PL that the dust cap should be replaced when the product is not in use
- Solutions for use with a nebuliser should be accompanied by clear instructions for use with various types of nebuliser (jet and ultrasonic) and steroids and antibiotics for use with a nebuliser should include a warning not to use with a facemask 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
- Product information should describe suitable solvents and diluents if supplied as a powder or concentrate for reconstitution; Products which require dilution should have this clearly marked on the immediate label along with any incompatibilities
- Where products consisting of a concentrate and solvent contain an overfill to compensate for liquid lost during the dilution process, labelling should indicate clearly that the entire contents of the solvent vial must be added to the concentrate vial
- Instructions for use for IV medicines should include clear instructions on the time over which the product should be administered or else a clear statement that a bolus dose may be given
- If a medicinal product has to be administered within a specific time after reconstitution or dilution this should be noted in product information
- Information on the appropriate dilution of solutions should be included in the SmPC and products requiring dilution require a Technical Information Leaflet (TIL) for use by HCPs to accompany the PIL; information on dilution should be described in the TIL.

General considerations

- Medicines for acute use in emergency situations should be presented in a ready-to-use format without the need for measuring of doses or solutions
- Where a single substance is available as different branded products or where different strengths have different indications, product information should highlight clearly any differences in posology (e.g. daily vs weekly administration of insulin analogues), composition (e.g. different excipients[30], some of which such as milk proteins, peanut oil may cause allergies), or strength (hybrid applications).
- Biosimilar products should be clearly differentiated from each other by use of distinguishing packaging and prescribed by brand name rather than by INN to minimise inadvertent switching between products and to allow for effective Pharmacovigilance.

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