Medication Errors : EU regulatory initiatives on risk minimisation and error prevention

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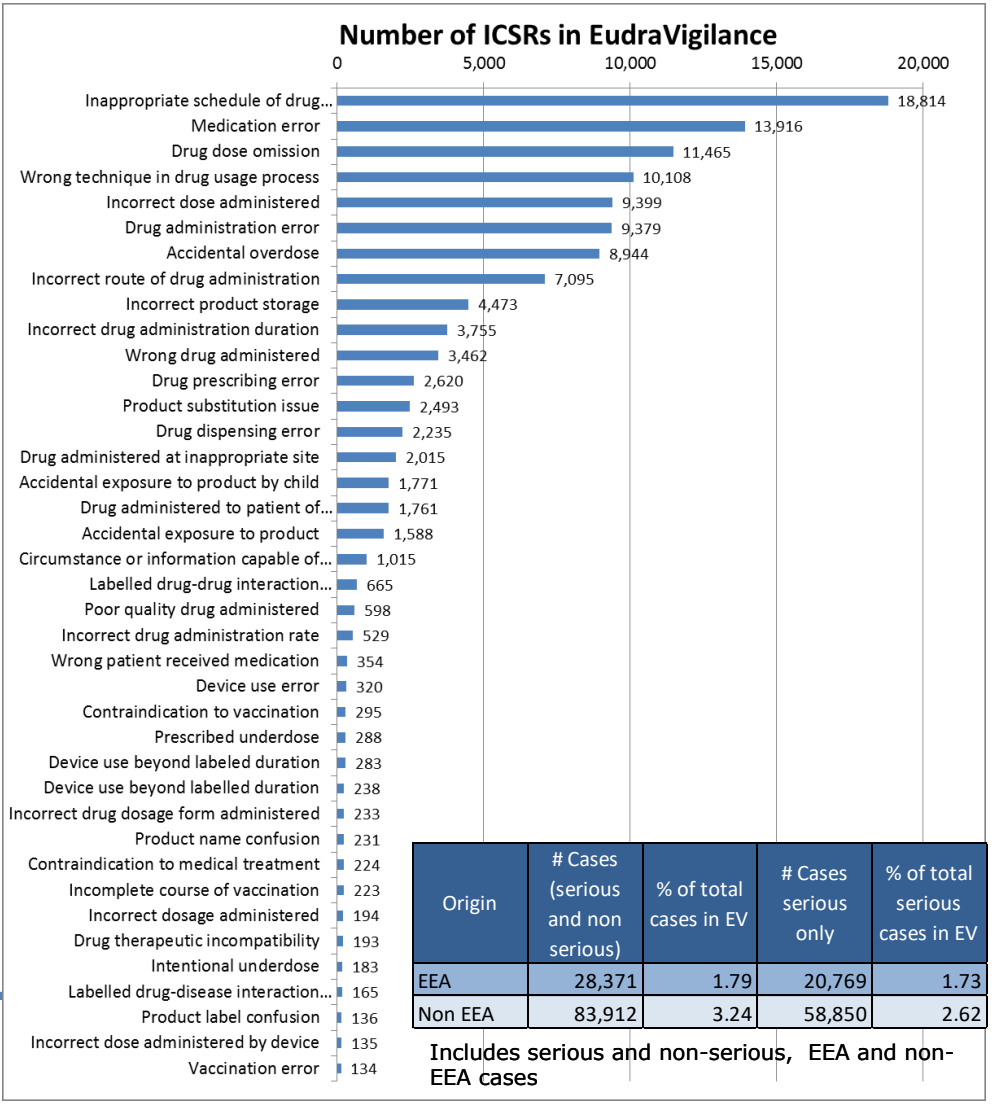
Background

- Medication errors (ME) are an important cause of morbidity and mortality and many errors are preventable
- EU pharmacovigilance legislation requires
  - Reporting of ADRs associated with ME to EudraVigilance;
  - Member States to liaise with national patient safety organisations for exchange of information on ME;
- Key deliverable of 2013 HMA action plan: **Good Practice Guide (GPG) on Medication Errors** developed by EU regulatory network with focus on
  - **recording, coding, reporting and assessment of ME (GPG I)**
  - **risk minimisation and prevention of ME (GPG II)**,

EudraVigilance reporting

10 most commonly reported **MedDRA preferred terms (PT)** (31/08/15):

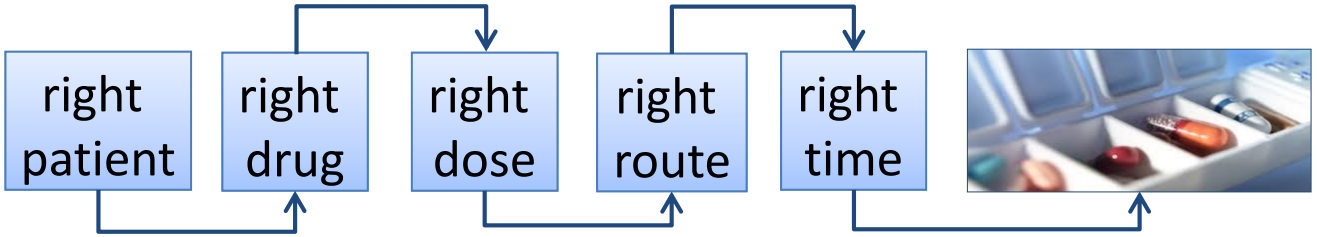
1. Inappropriate schedule of drug administration
2. Medication error
3. Drug dose omission
4. Wrong technique in drug usage process
5. Incorrect dose administered
6. Drug administration error
7. Accidental overdose
8. Incorrect route of drug administration
9. Incorrect product storage
10. Incorrect drug administration duration



Origin	# Cases (serious and non serious)	% of total cases in EV	# Cases serious only	% of total serious cases in EV
EEA	28,371	1.79	20,769	1.73
Non EEA	83,912	3.24	58,850	2.62

Includes serious and non-serious, EEA and non-EEA cases

What is a medication error?



Medication errors involve the failure to uphold one or more of the five “rights” of medication use, but may also involve

- dose omission
- dispensing or use of expired medication
- use of medication past the recommended in-use date
- dispensing or use of an improperly stored medication
- use of an inappropriate dosage form or administration technique inconsistent with the SmPC/PIL
- instructions for use of cartridges and/or prefilled pens not followed
- etc.

Definitions and Classification ❶

- **Medication error**

  A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (Good Practice Guide);

  – *Drug treatment process* includes **prescribing**, **storing**, **dispensing**, **preparation** for administration and **administration** of a medicine in clinical practice;

  – *Failure* means human error or process/system mediated failure rather than lack of efficacy of a drug;

  – The error is *unintended*. Intentional overdose, off-label use, misuse and abuse as defined in GVP Module VI are different concepts to be distinguished;

Definitions and Classification ❷

- **Potential error**

  A potential error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient (GVP Module VII.B.5.9);

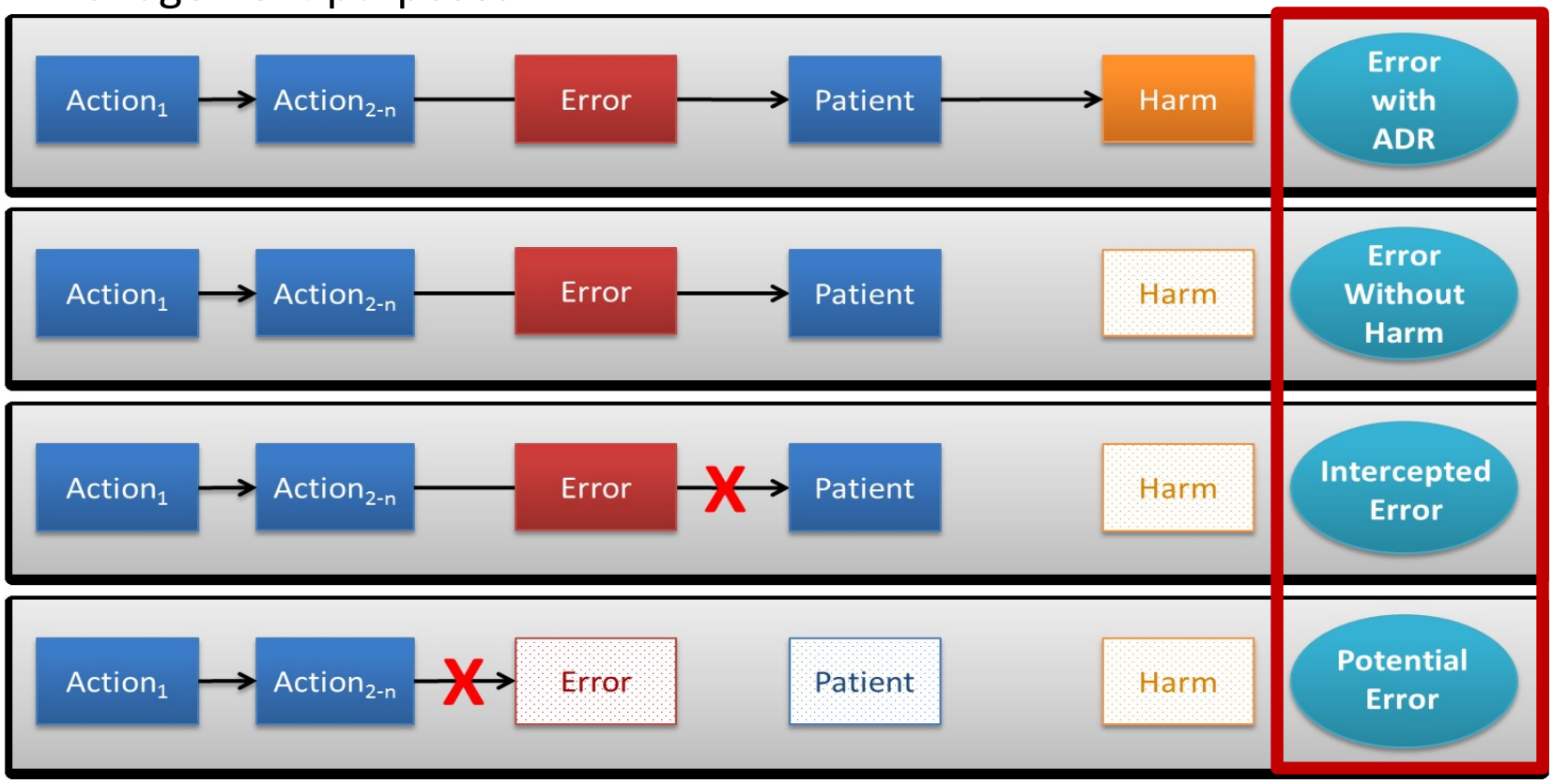
- **Intercepted error**

  An intercepted error indicates that an intervention caused a break in the chain of events in the treatment process before reaching the patient which would have resulted in a potential ADR (Good Practice Guide).

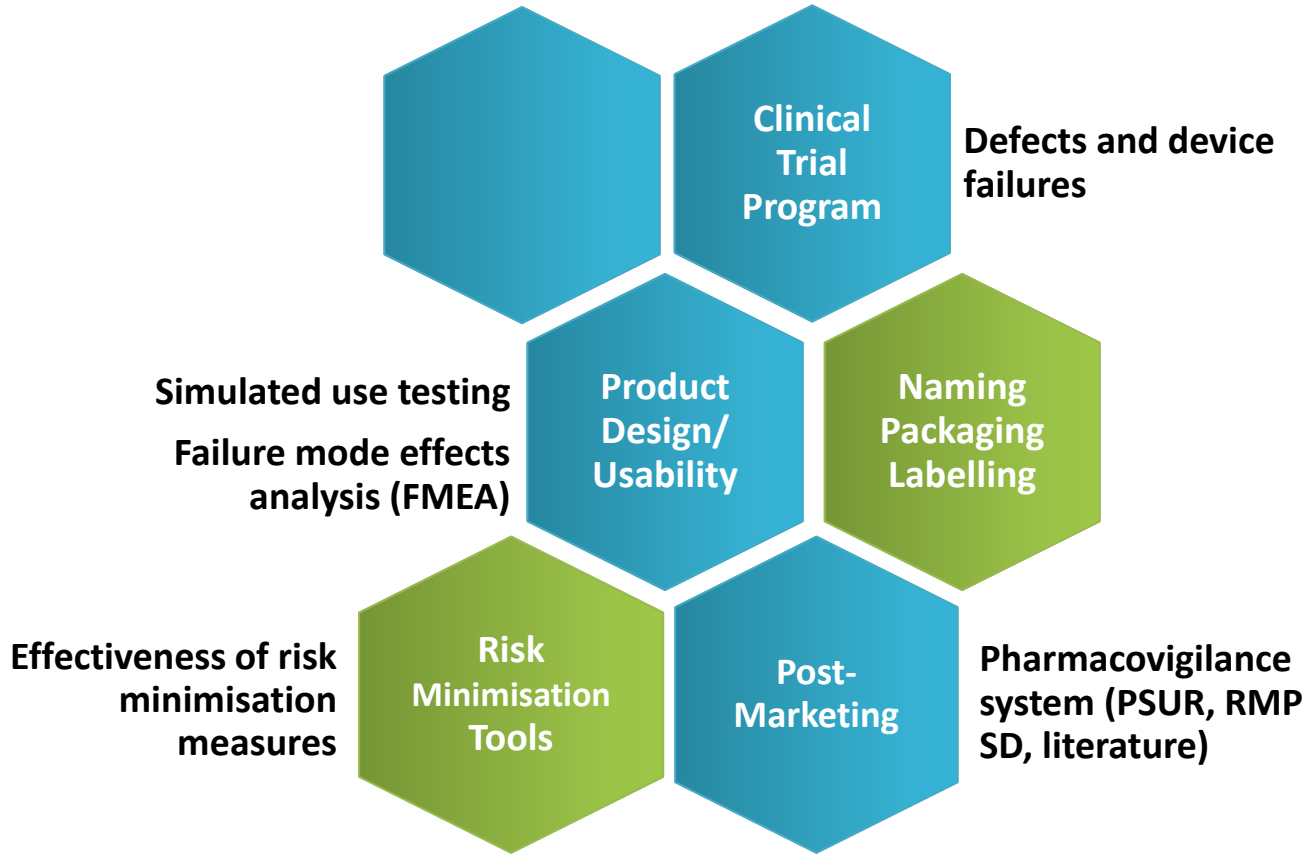
  – The intervention has prevented actual harm being caused to the patient, e.g. a wrongly prepared medicine was actually not administered to the patient because the error was noticed by the nurse.

Definitions and Classification ❸

- MEs should be **recorded and classified** for pharmacovigilance and risk management purposes:



Product life-cycle approach



Typical errors during development

Consider the **risk of medication errors** in relation to

- New product in **same or similar indication as marketed product** or significant changes to existing MA;
- **Product design** (e.g. drug delivery device, pharmaceutical presentation, posology, preparation for administration etc.)
- **Packaging** (e.g. small font size, absence of information or multiple dosages of IMP in same package)
- Multi-language **labelling**

Risk analysis of **use-related errors** during CT programme may include:

- Available treatment options and potential for confusion/mix-up with existing products (e.g. new high versus standard strength insulin)
- Similarities in posology, appearance, method of administration, strength and packaging (product livery, colour branding etc.);
- How the product will be used in real life conditions (with or without supervision of HCP/carer)?

Typical post-marketing errors

Most errors occur under **real-life conditions** at various stages of the treatment process:

- **Prescribing** – clear and legible instructions with correct patient, product, pharmaceutical form (e.g. immediate or modified release), strength, detailed dosing instructions, length of treatment etc.)
- **Dispensing** – correct selection of product (mix-up of similar product names and/or packaging or pharmaceutical form) both in community and hospital pharmacy
- **Storage** – correct temperature, humidity, expiry date
- **Preparation for administrat**ion – parenteral products requiring dilution or reconstitution, compatibility with diluents, infusion time, route of administration (IV, SC, IM) etc.
- **Administration** – correct dose units and times, conditions etc.

Product quality and device issues

- **Product quality issues** are abnormalities that may be introduced during manufacturing, labelling, packaging, shipping, handling or storing process;
  - To be distinguished and carefully evaluated if they fall in the definition of a ME (e.g. accidental underdose of antibiotic was administered because the lines on the dropper were hard to read which lead to ME);
- **Drug delivery device issues** (e.g. errors with pre-filled injector devices) are relatively common and usually related to wrong use of the device not in line with instructions for use (unclear, complex instructions etc.) with clinical consequence for the patient related to the drug;

High risk groups - paediatrics

Consideration for paediatric patients

- Due to **change in body surface area, body weight and size** depending on degree of development (particularly quickly in neonates) dosing errors are most common;
- **Pharmacokinetic profile** during early childhood also changes quickly which contributes to over- but also unde**r-doses**;
- Dosing instructions are often by body weight rather than age in months or years which requires **dose recalculation**;
- Risk of **dilution/reconstitution errors** in absence of appropriate paediatric formulations with medicines authorised for adults only;
- Dosing issues with liquid formulations if no or **wrong oral dosing device** (e.g. syringe) is provided and the liquid formulation exists in different strengths;
- **Accidental ingestio**n by children is also common, therefore childproof closure systems and primary packaging should be considered;

High risk groups - elderly

Considerations for the elderly

- Polypharmacy in the elderly patient is a common cause for mix-ups and administration errors;
- Difficulties in handling products (opening bottles, blisters, swallowing tablets/capsules, dividing tablets or counting drops, use of asthma inhalers etc.);
- Impaired eye sight (e.g. difficulties reading labels, dialling insulin units on pen or administration of eye drops) leading to errors;

- Patients with low literacy have difficulties following the instructions for use (i.e. use of pictograms and diagrams to visualise the correct use of the product is preferred);

Methodologies ❶

Usability studies

•**Simulated use testing** (=human factor/usability studies) with focus on design of product and user instructions under realistic conditions to indicate need for design or labelling changes

- Where design is complex (e.g. several dilution steps, administration device etc.) validation under actual conditions of use

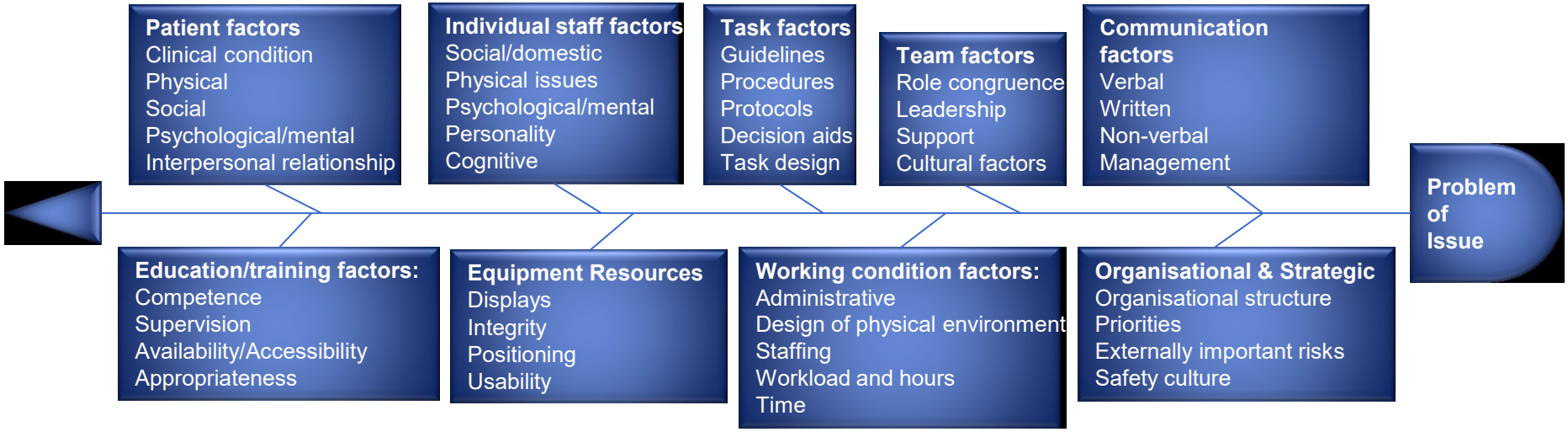
•**EU harmonised standards**, e.g.

- ISO 14971 – Medical Devices - Application of risk management (identify hazards and estimate and evaluate associated risks, to control these risks, and to monitor the effectiveness of the controls e.g. for pre-filled insulin pens) (http://www.iso.org/iso/iso_catalogue/catalogue_ics/catalogue_detail_ics.htm?csnumber=38193)
- IEC62366 - Medical Devices – Application of Usability Engineering to Medical Devices (http://www.iso.org/iso/catalogue_detail.htm?csnumber=38594)
- EN ISO 13485 – Quality management system

Methodologies ❷

Root cause analysis (RCA) is a structured method to analyse adverse events derived from errors with the aim of:

- Conduct RCA for any serious ME in the post-marketing setting
- Identification of *active* errors (errors occurring at the interface between humans and complex systems) and *latent* errors (hidden problems in healthcare delivery).
- RCA investigation follows 'fishbone diagram' - lessons learnt to reduce the likelihood of future errors:



Assessing the risk of ME ❶

Some **guiding questions** to assess likelihood of ME:

- *Are labelling and instructions for use clear and unambiguous (e.g. regarding reconstitution, parenteral routes of administration, dose calculation)?*
- *How is the product used in common practice? Is the product administered at the same time as other medicinal products by the same hazardous route?*
- *Is there a need for visual (or physical) differentiation between strengths of the same medicinal product and other products containing the same active substance on the market with formulations which are not bioequivalent?*
- *Is the product used by a visually impaired population (e.g. diabetes, colour blind people, etc.)*

Assessing the risk of ME ❷

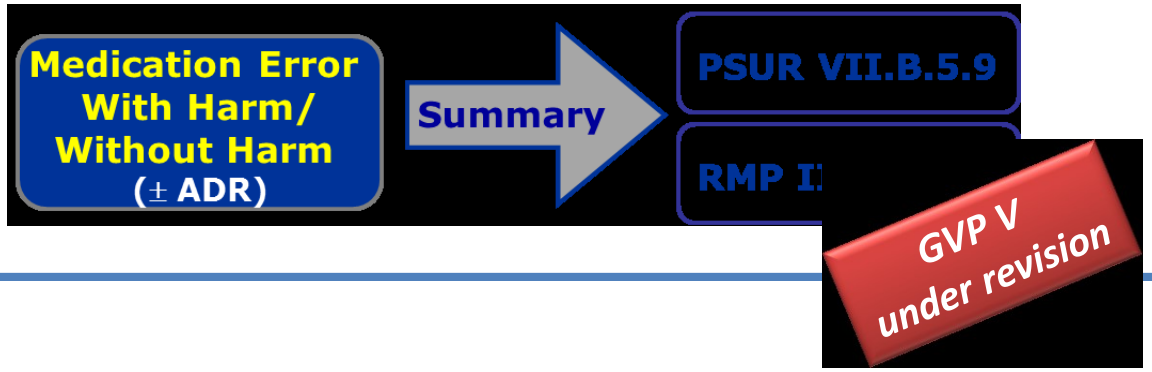
- *Is there a risk of accidental ingestion or other unintended use by children?*
- *If the formulation or strength of a product is being changed, is there a risk of confusion between old and new product in clinical practice?*
- *Are changes to the presentation, pack size, route of administration or release characteristics of the medicinal product associated with potential for mix-ups/ confusion?*
- *If the product is administered with a medical device (integrated or not) are there any safety concerns related to medical device malfunction (e.g. blocked needle, inhaler malfunction etc.)?*

GPG II Annex 1 - sources of error related to product design

Medication error as safety concern?

Inclusion of **ME as safety concern in RMP** depends on evidence:

- **Identified risk** if ME is associated with (serious) harm to patient (i.e. ADR) with impact on B/R or high number of occurrences (clear trend or pattern);
- **Potential risk** if consequences for patient are unclear or evidence for harm is lacking but error occurred during CT programme and/or post-marketing (i.e. ME with/without harm, intercepted error, potential error) and requires further investigation;
- Decision should be based on PSUR data and evidence from CT programme/DSUR;



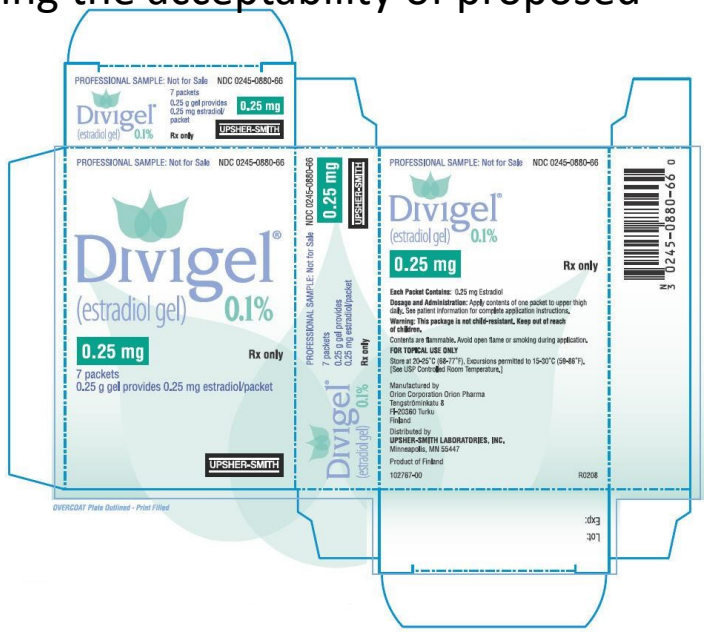
Tools for routine error prevention

Naming

- Name of the medicine (invented name, strength and pharmaceutical form) to appear prominently across the labelling with large font type on front panel;
- Avoid look-alike and sound-alike name with existing invented names to avoid confusion in print, speech and handwriting;
- Name Review Group (NRG) is reviewing and checking the acceptability of proposed (invented) names for the centralised procedure;

Labelling and pack design

- Pack design to ensure **critical information** necessary for the safe use of medicine is legible and easy to assimilate:
  - Name
  - Dosage unit (strength)
  - Pharmaceutical form
  - List of excipients
  - Method/route of administration
  - Warnings to keep out of sight of children
  - Expiry date, batch number
  - Contents by weight, volume or units
    Special storage or disposal conditions
    Information in Braille



Tools for routine error prevention

Labelling - colour coding

•Colour coding products of the same manufacturer ('trade dress') may help to distinguish and identify products correctly;

•Colour matching where colour is used to match up various components (e.g. solvent + concentrate) for multipart medicines may be considered;

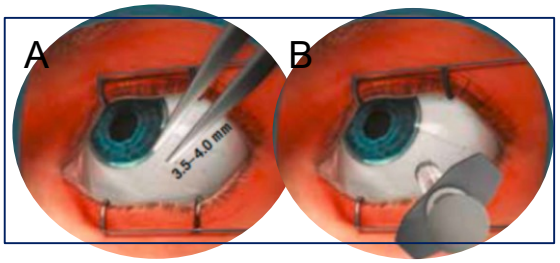
→ However, colour coding conventions do not exist and use of colour should be restricted to a manufacturer's product line if distinguishable;

- Colour/increased font size to highlight different strengths
- Colour to highlight warnings on primary packaging label

Tools for routine error prevention

SmPC and PIL

- Package leaflet must be user-tested and format tailored to patients who will use the medicines (e.g. large print for visually impaired patients)
- Clear posology/instructions for safe use in SmPC 4.2
- Warnings in SmPC 4.4
- Use of illustrations and pictograms if applicable (e.g. pen devices, inhalation devices, IVT injections) in SmPC/PIL (and educational materials)
- Internet training materials (e.g. for insertion of contraceptive implants)
- Regulatory agency website communication (e.g. EMA communication on medication errors on EPAR pages)



Additional risk minimisation tools

Patient and/or HCP educational material (GVP XVI)

- Dear Healthcare Professional Communication (DHPC)
- Patient/healthcare professional information leaflet/brochure
- Healthcare professional checklist/algorithm prior to prescribing
- Patient reminder card
- Patient alert card
- Safety communication with emerging technologies (e.g. smart phone application to report ADRs but also to receive safety alerts)
- Controlled access programme
- Other (e.g. pregnancy prevention programme)

GPG II Annex - design features to reduce risk of errors

Conclusion ❶

- Assess the **potential for medication errors at all stages of the product life-cycle**, particularly during product development and early marketing phase taking into account clinical practice;

- Discuss errors, their potential **cause(s)**, contributing factor(s) and possible **remedie**s in the RMP. For errors identified during the CT programme explain how these errors have been taken into account in the **final product design**;

Conclusion ❷

- **Adverse reactions** related to medication errors in the post marketing period should be discussed in the updated RMP and ways of limiting the errors proposed;
- To minimise the potential for medication errors:
  - Careful consideration of the **product name**, **drug product** design, **presentation** and **labelling** to **minimise the risk of mix-ups** between different products and different product presentations of the same brand;
  - **Product information** (SmPC and PIL) should inform healthcare professionals, patients and caregivers of the most appropriate use of the product with **clear instructions for use**.