

Medication errors: Development of prevention strategies for medicines and medical devices

Laurent Auclert

Chairman of the Pharmacovigilance Committee

EFPIA

- Medication errors defined as “occurring while the product is the control of the healthcare professional, patient or consumer” are closely related to the health care system in which the product is used
- Situations at risk of medication errors
 - Hospital/institutions
 - Complex products and
 - Complex medication administration processes
 - Devices for self-administration by patient (e.g. insulin pens)
 - Vulnerable populations: elderly, children, illeliterate, visually impaired

A complex medication administration process....



Product = Perfalgan (paracetamol) Intraveinuous

Issue = confusion between mg and mL leading to administration of 10 fold the prescribed dose
E.g.: for a patient weighing 10 kg the dose is **75 mg** (i.e. **7.5 mL**), **75 mL** of solution administrated (x 10)

Risk = Liver damage and death

Dec 2009: French Agency enquires about 21 overdose cases in neonates, 1 fatal, due to Medication Error related to the confusion between mg and mL.

Q1 2010: Agreement with MAH to implement the Risk Minimization Measures (RMM) in European countries

- Distribute a DHCP letter
- Distribute a Poster reminding the posology in neonates/infants
- Increase the font size « 10 mg/ml » on the 50 mL vial
- Assess the feasibility of a lower strength presentation

Jan 2011: MAH reports the number of overdose cases due to the confusion between mg and mL in paediatric patients

	UK n= 11	France n=10	Total n= 24
Before RMM	13	10	23
After RMM	1	0	1

Mar 2012: Additional RMMs in Europe



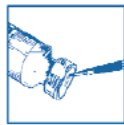
- Section 4.2 of the SmPC and PIL: Dosing table, New recommendations in children ≤ 10 kg
- Labeling wording update to keep only the essential information
- MAH's commitment for a Feasibility study to develop of a lower strength pediatric presentation
- Distribute a DHCP letter
- Distribute a Poster and Dosing Guide Strip
- Effectiveness:
 - Monthly review of MAH safety database
 - Quarterly Cumulative case count update to French HA

Launch of the new product design to simplify the medication administration process

Before: 2-vial Taxotere®



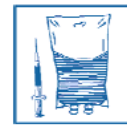
Taxotere® 40 mg/mL



Taxotere® 10 mg/mL
(after initial dilution)



Add into infusion solution



Now: 1-vial Taxotere®



Taxotere® 20 mg/mL



Add into infusion solution

(No initial dilution)

The introduction of the new formulation creates a risk of error during the period of switch

Communication/education to anticipate potential medication error risk

AVANT
ancienne concentration de la solution à diluer
= 10 mg/ml



MAINTENANT
nouvelle concentration de la solution à diluer
= 20 mg/ml





**NE PAS MÉLANGER L'ANCIENNE FORMULATION DE TAXOTERE® 10 mg/ml
A LA NOUVELLE FORMULATION DE TAXOTERE® 20 mg/ml DANS UNE
MÊME POCHE POUR PERFUSION**

Leaflet provided to hospital pharmacists: visual aids, instruction for replacing the stored products

insulin pens = drug delivery systems

Use errors

- Inadequate product differentiation
 - Within a product line or across similar products
- Unusual or unexpected device operation
 - E.g., needle stick injuries due to user holding device upside-down
- Confusing or complex device controls
- Electronic display legibility or message clarity
 - E.g., font size and visual contrast
 - E.g., confusion from lack of preceding zeroes (.5 mg instead of 0.5 mg) or presence of trailing zeroes (5.0 mg instead of 5 mg)



mitigation of medication error risk in the product design

Following reports of **mix-ups between different types of insulin**, manufacturers have improved differentiation within their product line



**Color
differentiation**



**Tactile
Differentiators**

Items to be considered pre-marketing (GVP V)

- **Naming**
 - “Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed Through the Centralised Procedure”,
- **Presentation** (e.g. size, shape and colouring of the pharmaceutical form and packaging),
- **Instructions for use** (e.g. regarding reconstitution, parenteral routes of administration, dose calculation)
- **Labelling**
 - “Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use”

- Product labeling, instructions for use, health care provider and patient education may not be sufficient to overcome product design features that predispose to errors
- Manufacturers have not been requested to systematically consider the potential for medication errors in the **product design**, naming, packaging, labeling pre-marketing
 - Except when combined with drug delivery device
 - Corrections of errors detected post-marketing
- Regulations are emerging
 - EU: 2010 legislation and subsequent EMA GVP
 - USA: FDA guidances under development

The FDA initiative - background

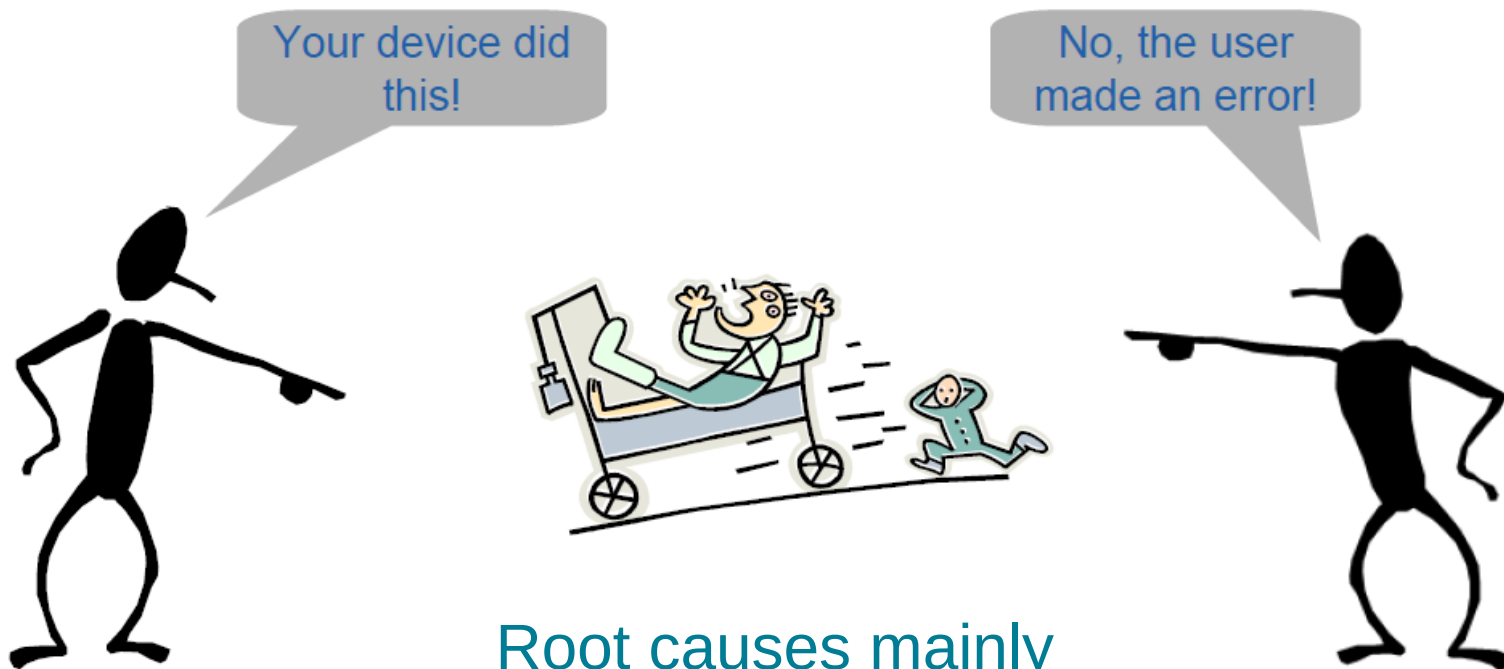
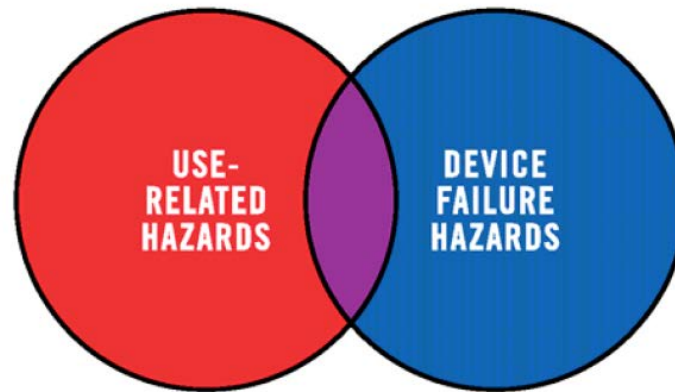
- 2000 – IOM report : 7,000 deaths annually attributed to medication errors in the US. Recommendations:
 - FDA to develop and enforce standards for the design of drug packaging and labeling that will maximize safety in use; and
 - Pharmaceutical companies to test proposed drug names to identify and remedy potential **sound-alike and look-alike confusion** with existing drug names.
- 2006 – IOM report: labeling and packaging issues cause 33 % of medication errors, including 30 % of fatalities from medication errors
 - Product naming, labeling, and packaging should be designed for the **end user** = the provider in the clinical environment and/or the consumer
 - FDA should incorporate better principles of cognitive and human factors engineering to address issues concerning information presentation in labeling and nomenclature

FDA is writing 3 guidances to minimize medication errors:

- ❑ Design of Drug product and container closure*
 - ❑ Design of labels, carton labeling, packaging configuration
 - ❑ Drug product nomenclature
-
- Based on systems approach, capitalizing on experience with **Medical Device design** optimization through human factors analysis
 - To be applied
 - Before initial approval – start early in the development
 - Prior to subsequent product change (new formulation, dosage...)

* Draft guidance: safety considerations for product design to minimize medication errors, Dec 2012

Medical Device Design experience



Root causes mainly
found in user interaction

Considerations at early stage of product design

(draft FDA guidance)

- **1. End users** (Patient, patient's caregiver, prescribing physician, nurse, pharmacist, pharmacy technician, any individual involved in procurement, stocking, storage and administration)
 - who are they? Differences in age, education, training?
 - Complexity of the proposed product? Multiple steps to deliver? Manipulations? User training needed?
 - Specific skill set/knowledge needed? Is knowledge gained from previous related products?
 - Etc...
- **2. Environments of use**
 - In what environment might the product be used? Lighting levels? Noise levels? Distractions?
 - What storage? Similar products used in the environment?
 - Etc...

Considerations at early stage of product design

(draft FDA guidance)

- **3. Drug Product - User interface**
 - Evaluation of product performance and use interactions cannot rely only on controlled clinical trials because it does not reflect “real world”
 - Need to test the design using proactive risk assessments, based on lessons learned from problems that have occurred with similar products
 - With the product itself
 - Or with the container (vial, ampule, tube, blister pack..) or the closure (cap, stopper, seal)

Proactive risk assessments

- FDA recommends two methods:
 - Failure Mode and Effects Analysis
 - Simulated Use testing
 - Involve representative participants using early or final drug product designs and their packaging and labeling in realistic situations
 - Direct observation, subjective use feedback, discussions of reasons for errors or failures, manual and automated user performance measures.
- Industry suggests other Human Factor Engineering methods that have shown greater efficiency (e.g. PCA analysis)

The PCA Model to Identify Use Error Potential

Perception (sense)

user is unable to

- **SEE** [info on screens, labels, bags, tubing, lights,]
- **HEAR** [alarms, warnings, clicks, beeps, melodies]
- **FEEL** [clicks, detents, vibrations, screen, etc.]

Under conditions of..

- All lighting, noise profiles
- Fatigue/disease states
- Gloved operation

Cognition (think)

user is unable to

- **INTERPRET** {distinguish, recall meanings of input}
- **KNOW** (vital information to do task, recall process)
- **COMPUTE** (transform, etc)
- **DECIDE** (choose action, judge status, etc.)

Under conditions of..

- Multi-tasking workload
- Stress
- Fatigue/disease states

Action (respond)

user is unable to

- **TOUCH** {finger pointing}
- **PRESS** (buttons, switch)
- **TWIST** (buttons, switch)
- **FOLLOW** (track object)
- **APPLY FORCE** (open battery comp, luer con.)
- **MANIPULATE** (dexterity)

Under conditions of..

- Gloved operation
- Fatigue/disease states
- Chronic injuries (RSI)

Formative Evaluations

- While the device is still under development
 - Include representative end users
 - Test simple product mock-ups or early prototypes
- Done early in the design process
 - At this stage use-related problems can be addressed more easily and less expensively
- Best when performed iteratively
 - Repeat until the device is optimized and ready for human factors/usability validation testing

Risk Mitigation

- Develop a risk mitigation strategy
 - Modify interface design, user instructions, and/or training to address the problems found
- Re-test to demonstrate effectiveness of mitigation
 - Not sufficient to simply state that the device will be modified or that mitigations will be implemented later
- Residual risk is acceptable if discussed, reasonably limited, not capable of elimination or further reduction, and benefits outweigh it

Human Factors/Usability Validation

- Demonstrates and provides evidence that a medical device, as designed, can be used safely and effectively:
 - By representative intended users
 - Under realistic use conditions
 - For critical (high-risk) and essential tasks
- Objective and subjective data:
 - Use errors and failures are observed and recorded
 - User opinion and feedback is collected from users afterward, particularly related to any use problems

Conclusion (1)

Strategy for prevention of medication errors

- Starts with an appropriate collection of actual cases to learn from experience
- Root Cause Analyses of actual cases
 - Serve both pre- and post-market safety assessments
 - Medication errors are more related to breakdown(s) in the medication-use system than with user's competency
- Solutions require standards for the design of drug naming, packaging and labeling to be applied across the medication system(s)
- Engagement of all contributors ('end users') involved in the process of designing/modifying a product

Conclusion (2)

Strategy for prevention of medication errors

- Use Human Factor Engineering method to design a product
- Product design can benefit from IT developments: electronic prescribing, coding to track the product, audio-guide...
- Beyond product design, packaging and labeling, communication and education of the end users is critical
- An informed patient is one of the best safeguards against medication errors