The European Medicines Agency’s review process of medicines’ labelling and packaging to prevent risks of medication errors

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Presented by: Monica Prizzi
Product Information Quality Service/European Medicines Agency
Introduction

• Legal Basis

• Product Information Quality Service

• Checking process of mock-ups and specimen of outer/immediate labelling and package leaflets

• Interactions with stakeholders

• Conclusions
Legal basis

European legislation:

- Title V of Directive 2001/83/EC.
  - Art.54,55 and 59 lay down information to appear on outer/immediate packaging and on package leaflet.
  - Art.61 states that one or more mock-ups of outer/immediate packaging and package leaflet is submitted to the Agency when marketing authorisation is requested.

- Guideline on the readability of the labelling and package leaflet of medicinal products for human use. (Rev.1, January 2009)
  - Sets out helpful advice on the presentation of the content of the labelling and package leaflet and on the design and layout concepts to ensure that medicines can be used safely and appropriately.

- Guideline on the Packaging information of Medicinal Products for Human Use authorised by the Community” (Rev.14, July 2013)
  - Provides, in particular, information on the requirements by some Member States to appear on the outer packaging “Blue Box” (Art.57 of Directive 2001/83/EC).
Legal basis

• Checking process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the centralised procedure (Rev.1, March 2013).

  ➢ **Review process** developed by the Agency in 2007 detailing the **checking** process of the **printed packaging materials** for outer/immediate **labelling** and **package leaflet** for centralised products.

• Product information Templates

  ➢ Set out the **standard headings** and indicate the most commonly used **standard statements** and terms in all the official European Union **languages** (plus Norwegian and Icelandic).

**Other reference documents:**

• National Medicines Regulatory Agencies guidance.

• Publication and guidance published by organisations focused on patient safety and safe medication practice.

  ➢ MHRA best practice guidance on labelling and packaging of medicines (June 2003)
Product Information Quality (PIQ) Service

PIQ covers 3 main areas:

- Quality Review of product information (content and linguistic review of the summary of product characteristics (SmPC), the labelling and the package leaflet).

- Mock-ups & specimens of outer/immediate labelling review (packaging layout and readability of information).

- Name Review Group secretariat (Review of proposed product names).

=> Part of routine risk minimisation measures.
Key findings

- **Problems** with the **labelling and packaging** have been associated with a high number of medication errors.

- The **labelling and packaging** ensures that the critical information necessary for the safe use of the medicines is **legible, easily accessible** and that users of medicines are assisted in assimilating this information so that **confusion and error are minimised**.

- Correct identification/use of medicines relies on **good quality labelling**.

* Guideline on the readability of the label and package leaflet of medicinal products for human use.
Mock-Ups and Specimens review - **Definition**

- **Mock-up**: copy of the flat artwork design in full colour (A3/A4 format).

- **Specimen**: samples of the actual printed outer and immediate packaging materials and package leaflet (i.e. the sales presentation).
Mock-Ups and specimens review - **Procedure**

- **Mock-ups** are reviewed in parallel to the **scientific assessment**:
  - Submission of **English** and **multi-lingual** ("worst case") colour mock-ups
  - For outer and immediate packaging
  - For each pharmaceutical form and strength
  - For each container type (e.g. blister, bottle, vial...etc.).

- **Specimens** reviewed **before launch**:
  - Submission of one set of the **relevant specimens** of outer and immediate packaging and package leaflet
  - To be provided for review at the latest **15 working days before launch**;
  - For each pharmaceutical form and strength
  - For each container type (e.g blister, bottle, vial...etc.).
Mock-Ups and specimens review – **Timeline (New applications and extensions)**

- **Day 1 Submission**
- **D120 List of questions**
- **D121 clock restart**
- **D150 Joint assessment report**
- **D180 List Outstanding issues**
- **Day 210 Marketing authorisation**
- **Product launch**

**1st mock-ups review**
- Identification of issues at an early stage
- Liaise with assessors
- Liaise with experts

**2nd mock-ups review**
- Review of all outstanding comments (on average **3-4 rounds of mock-ups reviews**)
- Review of specimens prior to launch

**Changes to labelling prior to specimen printing – shorter specimen reviews – facilitate faster launch**
Mock-Ups and specimens review – **Timeline (post-authorisation procedures)**

- **Renewals**
  - Specimen review of all marketed product presentations

- **Transfers**
  - Mock-ups review of all presentations (case by case)

- **Other post-authorisation procedures**
  - Mock-ups and/or specimen review on a case by case basis and when the overall design and readability is affected

Packaging changes not part of any regulatory procedure and affecting overall design and readability

Mock-ups and/or Specimen review
Mock-Ups and Specimens review – **Who** is checking?

- We are a small team.

  ➢ Some statistics (2007 to July 2013)*:

![Bar Chart](chart.png)

*based on number of reviews.
Mock-Ups and Specimens review – **What do we check?**

- General check from the **viewpoint of readability**:  
  - Ensure that the **critical/important information** for the safe use of the medicine is **legible** and clearly mentioned on **prime spaces** of the labelling to minimise the occurrence of medication errors.

- **Focus**:
  - Presentation of critical information (name of medicine, strength/concentration, pharmaceutical form and active substance)
  - Special warnings
  - Differentiation between strengths
  - Font sizes, positioning of the text, line spacing
  - Use of colours/pictograms/logos
  - Overall lay-out and design

* No detailed linguistic check (i.e. no checking of the actual text.)
Mock-Ups and Specimens Review – **How do we check?**

**TRADE**
100 microgr.
concentrate
infusion

**Active su**
400 microgr.

4 x 4 ml vials

**TRADENAME**
100 micrograms/ml
concentrate for solution for infusion
Active substance
200 micrograms/2 ml

Each ml of concentrate contains to 100 micrograms
Also contains sodium chloride, water for injections.

Read the package leaflet before use.
Keep out of the reach and sight of children.
Should be used immediately after dilution.

5 x 2 ml ampoules

**TRADENAME**
100 micrograms/ml
concentrate for solution for infusion
Active substance

4 x 10 ml vials

Blue box

**TRADENAME**
1000 micrograms/10 ml
Intravenous use

4 x 10 ml vials
Mock-Ups and Specimens Review – Example
Mock-Ups and Specimens Review – Examples
Mock-Ups and Specimens Review – **How do we check?**

- **Package leaflets**

  - Clear headings to help navigation
  - Folds not interfering with text readability
  - Use non-glossy paper
  - Length of the leaflet

  **User testing carried out in parallel to scientific assessment**

  **Critical information in bold**

  **Font size readability**

  **Use of non-justified text**

  **Contrast between text and background (Paper weight and colour)**
Mock-ups and Specimens review – **Challenging areas**

- **Family design**
  - Similarity issues due to:
    - Use of same design
    - Use of defined colour coding
    - Same colour patterns used for different combinations of active substances.
    - Strengths and active substance or combinations of active substances not prominent enough

- **Pack design** is an important element of **patient safety** and **companies** should ensure that all their **products using a family design** are **identifiable** and are easily **differentiated** between them.
Mock-ups and Specimens review – **Challenging areas**

- **28 Member States (+ IS and NO)**
- **Information has to be identical in all the languages**
- **25 languages**
- **Tri-lingual packaging legal requirement (Belgium)**
- **Bi-lingual packaging legal requirement (Finland)**
- **All languages packaging (e.g. orphan medicines)**
- **Different languages combination can be used**
- **Size of the packaging might allow inclusion of many languages**

**Multilingual packaging**
Mock-Ups and Specimens Review – Multilingual packaging

- All these readability principles can be very difficult to apply on multilingual packaging.

- The general readability is affected by the decrease of the font size, dense blocks of text, less line spacing and less prominence of the critical information.

⇒ The same principles applied to the single language packaging are valid.

⇒ The readability and the clear and unambiguous identification of the medicine should be ensured.
Mock-Ups and Specimens Review – Examples
Mock-Ups and Specimens Review – **Multilingual packaging**

- **Several strategies are available:**
  - Use of innovative labels
    - Display of one language per panel
    - Use of English or Latin for the active substance
    - Use of short standard terms (pharmaceutical form, route of administration, container)
  - Use of standard abbreviations
  - Text simplification (Art. 63 of Directive 2001/83/EC)*
  - Language exemption (Art. 63 of Directive 2001/83/EC)*
  - To have thorough assessment of the text that will be displayed

*Products not intended to be delivered directly to the patient and orphan products
Mock-Ups and Specimens Review—**Availability issues**

- **Labelling** can be **one of the main obstacles** preventing marketing of medicines in **small markets**.

- Need to **balance** between **multilingual** packaging **restrictions** and **availability**: patients, physicians, pharmacists need medicines.

  ⇒ Need to **develop guidance for multilingual** labelling.

  ⇒ All available **guidance** usually **refers** to **single-language** packs leading to request for **text simplification** to accommodate multilingual packs.

  ⇒ Text simplification **raise concerns** amongst some **Member States** where single language packs are used.
Mock-Ups and Specimens Review—**Interactions**

Who do we involve?

- Patients and Consumers
- Healthcare professionals
- Patient safety and safe medication practices organisations
- Member States
Mock-Ups and Specimens Review—*Interactions*

- As part of the **routine risk minimisation measures**, the Agency reviews:
  - Statutory information included in the **product information** (Summary of product characteristics (SmPC), the labelling and the package leaflet)
  - Readability of the **packaging**
- However, sometimes there is also scope to further address the **practical aspects** of prescribing, dispensing and handling of the medicine to prevent potential medication errors.

Need for expertise
Mock-Ups and Specimens Review—Interactions

- **Member States, patients** and **healthcare professionals** are consulted during the product information and the packaging review:

  - **Member states (Quality Review of Document (QRD) group)**
    - Review of the product information (Linguistic review process)
    - On a case by case basis review of the packaging

  - **Patients:**
    - Review of the package leaflet
    - On a case by case basis review of the packaging

  - **Healthcare professionals**
    - Consulted when specific expertise is required (product information, packaging, educational material...etc.).
Mock-Ups and Specimens Review – Interactions

- The following are some of the areas were Member States, Patients, and Healthcare professionals were consulted:
  - Introduction of a new device/change of device
  - Introduction of a new pharmaceutical form
  - Inclusion of specific warnings
  - Introduction of a new concentration/new strength
  - Review of layout and readability in the context of multilingual labelling
  - Confusion due to unclear instructions for use
  - Expression of strength issues (e.g. injectable)
  - Qualitative & quantitative composition – active substance (salt vs. base)
  - Completeness of package leaflet compared to SmPC
  - Labelling simplification (Art.63)
  - Potential for medication errors
Mock-Ups and Specimens Review—**Interactions**

- Our *experience* showed that the **biggest improvements** to the labelling/packaging were the **results** of the **collaboration** with healthcare professionals, patients and patient safety and safe medication practice organisations.

- Need to **strengthen** the **links** with all **stakeholders**.

- Especially work closely with **Patient safety and safe medication practices organisations**.

- **Respond** to reports from Patient safety and safe medication practices organisations (post-marketing):
  - Dosing errors reported due to expression of strength (Torisel)
  - Dosing errors reported due to active substance expressed as *base* rather than *salt* (Halaven)
Conclusions

• The correct identification/use of medicines relies on good quality labelling.

• The establishment of an interaction with stakeholders in the area of the review of the labelling/packaging is important in the prevention of medication errors.

• Further collaboration with stakeholders, including industry, to develop Safety guidelines on labelling and packaging is crucial.

• Despite the challenges, we are making significant progress in this area.

• The Agency is committed to actively engage with national competent authorities, patients, consumers, healthcare professionals, patient safety and safe medication practices organisations and industry to tackle the issue of medication errors.
Contacting the Agency

• For any queries related to the review of mock-ups and specimens: muspecimens@ema.europa.eu

• For any queries related to the work of the Agency: info@ema.europa.eu

www.ema.europa.eu
Grazie!
Merci!
Thank you!