

**Safety and usability of packaging and labelling:
assessment is required prior to marketing authorisation for all medicinal products,
not just for copies of existing drugs**

- *Poor packaging is a major cause of medication errors. In its response to the European Medicines Agency's public consultation on potential medication errors in the context of benefit risk balance and risk minimisation measures (1), Prescrire calls for the safety and usability of the packaging and labelling of new medicines to be assessed as part of the evaluation of marketing applications. Prescrire calls also for a re-examination of all the packaging of existing medicinal products.*

Summary:

- The draft position paper that the European Medicines Agency (EMA) released for consultation on 1st June 2012 is not about considering potential medication errors as part of the evaluation of all medicinal products before marketing authorisation is granted. It focuses on the risks generated by copies containing the same active substance as a medicinal product that is already marketed. The draft does not specify whether “umbrella” brands fall under the scope of this position paper, despite their dangers.
- The identification of potential medication errors should result in measures to prevent their occurrence. Yet the EMA simply asks that a "risk management plan" be put in place, providing hardly any additional risk-prevention measures beyond those required whenever marketing authorisation (MA) or a variation is granted.
- *Prescrire's* response to the EMA consultation details several concrete proposals that should enable health authorities to effectively reduce the risk of errors associated with medicines and related devices. *Prescrire's* two main proposals in order to effectively prevent preventable medication errors are that:
 - the safety and usability of the packaging and labelling of new medicines must be assessed as part of the evaluation of MA applications. Drug regulatory agencies must conduct this assessment and publish the results in a “medication errors public assessment report” well before the medicinal product is marketed;
 - European authorities and national medicines agencies must re-examine existing medicinal products since the packaging of medicinal products is too often poorly designed and conducive to errors. They should begin with packaging items most frequently implicated in medication errors. They should also use various opportunities throughout the medicinal product's life (when examining applications for a major MA variation, in case of expanded distribution (when a hospital-only medicine is made available in the ambulatory sector), on reclassification, or during worksharing procedures to assess paediatric data under Article 45 of the Paediatric Regulation of 2006).

**Safety and convenience of packaging and labelling:
assessment is required prior to marketing authorisation for all medicinal products,
not just for copies of existing drugs**

● ***Prescrire's response to the European Medicines Agency's public consultation on potential medication errors in the context of benefit risk balance and risk minimisation measures (1)***

The guideline on good pharmacovigilance practices defines medication error as “any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer” (2).

Pharmaceutical companies are encouraged to “take into account potential reasons for medication errors (...) during the development phase and during the design of a medicinal product for marketing”, as part of a future risk management plan, mainly taking into account the product's: name; presentation (including its pharmaceutical form and packaging); instructions for use (including reconstitution procedures, routes of administration, dose calculations); and labelling (2).

Prescrire's analysis of the EMA's draft position paper, which was released for consultation on 1st June 2012, is based on the experience we have acquired in analysing the packaging of medicinal products (3–7), viewing it as a preliminary and welcome move by the EMA to give greater attention to the risks of medication errors.

The proposed medication error risk assessment is insufficient and limited to “copies” of existing medicines

Contrary to the implication of its main title, the EMA's draft position paper is not about consideration of the risk of medication errors as part of the evaluation of every medicinal product before market introduction (1). It focuses on the risks generated by medicinal products “containing the same active substance [as an existing medicinal product] and similar in some other attributes such as appearance and/or name but different in strength, dosing, route of administration (...) that [are] presented in a different pharmaceutical form, a new administration device or [have] a different composition or [are] intended to be used in a different patient population or indication, etc.” (1).

The EMA's draft position paper intends to minimise the risks associated with such "copies" and variants of existing drugs through risk management plans.

What about umbrella brands?

Umbrella brands use the same brand name extension (e.g. "Doli°", "Nuro°", "Vicks°") on a range of products with different compositions. Their dangers are well documented (a).

But the EMA does not specify whether its position paper applies to the risk of confusion between medicinal products belonging to the same umbrella brand.

No systematic assessment of potential medication errors for every medicinal product

By focusing on the particular situation where confusion could arise between products containing the same active substance, i.e. on a predictable risk of medication error, the EMA avoids applying the kind of thorough, exacting methodology required to test for and detect all the risks of medication errors associated with a given medicinal product (8).

For this particular risk of confusion, the EMA proposes evaluating only the extent to which the new product differs from the existing product and the adverse effects that would ensue if an error occurred, but not the risks of error inherent to medicines that are already marketed (b). Furthermore, the EMA proposes weighing the potential benefits of the “copy” or variant of an existing medicinal product against its risks only when a “high” risk of confusion is identified. But the EMA does not propose a method for quantifying these risks.

No truly comparative assessment of risk-benefit balance

The risk-benefit balance of copies and other variants cannot be assessed unless methods are provided for quantifying expected benefits (e.g. fewer adverse effects or greater convenience) and comparing them with risks (e.g. the criticality of each type of medication error), which the EMA’s draft position paper fails to do (see our proposals below).

Risk management plans: insufficient and too late to prevent medication errors

The EMA has contented itself with asking that “risk management plans” be put in place, but they are produced too late and provide hardly any additional risk-prevention measures beyond those required whenever marketing authorisation (MA) or a variation is granted. These risk management plans merely involve:

- strengthening alerts and warnings on the SPC, package leaflet and labelling;
- and possibly, on a case-by-case basis, changing the name, testing the readability of package leaflets, and proposing different packaging designs, yet no practical evaluation is required of the effectiveness of measures to help users discriminate between the different products.

In summary

The measures the EMA is considering in order to improve the prevention of medication errors associated with copies and variants of existing medicinal products do not go much further than the information strengthening traditionally used by drug regulatory agencies and pharmaceutical companies. The EMA does not propose a method for evaluating these measures.

Rather than implementing risk management plans aimed at minimising the risks of certain medicines after their market introduction, errors would be prevented more effectively by systematically and rigorously analysing the risks of medication error and taking preventive action before market introduction (see our proposals below).

Prescrire’s 7 proposals to prevent the risks of error associated with medicines and associated devices

The packaging of medicinal products (outer packs, package leaflets, blisters, child-proof caps, etc.) is a fundamental part of a drug’s risk-benefit balance and a key factor in ensuring correct use and preventing medication errors.

Pharmaceutical companies that design packaging and the drug regulatory agencies that grant marketing authorisations must stop overlooking packaging, given its importance to patient safety and the correct use of medicines.

The poorly designed packaging of currently marketed medicines exposes patients to the risk of errors that could have been prevented. Identifying these dangers after market introduction is also more disruptive to pharmaceutical manufacturing than implementing modifications to minimise foreseeable risks before market introduction.

Health authorities (c) must have the means to effectively reduce the likelihood of errors related to medicines and associated devices, without passing the risk onto users.

● Proposal 1:

For new medicinal products, assess the potential for error associated with packaging and labelling as part of the evaluation of the MA application

In addition to evaluating the benefits and harms associated with the active substance, drug regulatory agencies must conduct a separate assessment of the risk of error associated with the medicine's packaging and labelling and publish their findings in a medication errors public assessment report, right from the earliest stages of the registration process, so that improvements can be implemented before the MA is granted (d).

To enable the health authorities to produce a medication errors risk assessment, pharmaceutical companies should provide a dossier including:

- an evaluation of the labelling (including the name), instructions for use, preparation and administration, and the associated devices, addressing their effectiveness in preventing medication errors in healthcare situations (cf. proposal 2 "Raise quality and safety standards for packaging");
- a prospective analysis of the risks of medication errors, to better quantify the danger to which patients might be exposed in real-life healthcare situations (cf. proposal 3 "Establish rigorous criteria and methods for assessing the risk of medication errors").

To perform this task effectively, drug regulatory agencies must strengthen their teams' resources and expertise in packaging analysis, by creating task forces dedicated to assessing packaging-specific risks and to developing new solutions for improving packaging safety and usability.

● Proposal 2:

Raise quality and safety standards for packaging

The EMA should take on board the many recommendations to improve packaging that have been put forward by *Prescrire* (9) and others, such as the Council of Europe (8), and in particular 7 general measures (numbered 1 to 7) and 4 measures specific to certain pharmaceutical forms (numbered 8 to 11):

- 1- The international nonproprietary name (INN) and dose strength must be prominently and legibly displayed on labelling and package leaflets to ensure that medicines are identified by their real name, the brand name having less prominence than the INN (application of the 2009 European Commission's guideline on the readability of the labelling and package leaflet of medicinal products for human use (Rev 1 ref. ENTR/F/2/SF/jr (2009)D/869));
- 2- The essential information must be clearly displayed on at least 3 surfaces of the secondary packaging (box), leaving adequate space to systematically add patient-specific information about the treatment, either handwritten or in the form of a "dispensing label";
- 3- Font sizes must be large enough to be read easily;
- 4- Clear descriptions of dose strength and concentration must be given;
- 5- All medicines whose doses are standardised must be supplied in unit dose presentations that are ready to use or administer;
- 6- Reject unintelligible multi-language packaging;
- 7- Evaluate graphics, pictograms and colours, mainly used to help users discriminate between different dose strengths of the same medicine, paying special attention to colour coding that might cause errors by providing a false sense of security;
- 8- Ban bulk bottles for tablets and capsules, beginning with substances that are fatal to children (e.g. *iron, methotrexate, quinine*) and orodispersible medicines;
- 9- Require each dose of tablets or capsules packaged in blister packs to be individually and fully labelled, and require a safety film on blister packs that contain particularly dangerous drugs (e);
- 10- Require a child-proof cap on bottles of oral liquid medicines, unless accidental ingestion has been shown to be harmless;
- 11- Require multi-dose oral liquid forms to be supplied with an appropriate dosing device of suitable

capacity and accuracy (such as an oral delivery syringe graduated in milligrams or units).

● **Proposal 3:**

Establish rigorous criteria and methods for assessing the risk of medication errors

Several of the Council of Europe's recommendations describe the principles and methods for assessing the risk of errors associated with trade names and packaging, based on user testing by healthcare professionals and patients in real-life healthcare situations (8). The report includes a safety assessment form for this purpose, which is very similar to the one used by the *Prescrire* Packaging Working Group (3,4). We urge drug regulatory agencies to use it systematically and improve it.

The principle of readability testing must be extended to all information on the packaging of medicinal products: the package leaflet (as already required by Directive 2001/83/EC as amended by Directive 2004/27/EC), but also the labelling on all packaging items (box, primary packaging, dosing device), including any information depicted graphically (pictograms, dosing schedules, signs and symbols). The use of any graphical information that has not been evaluated or has been deemed unsatisfactory in tests should be prohibited.

Readability and user tests on packaging from the same commercial range are an effective way of detecting risks of confusion and medication error. They should be performed by an adequate number of users from the population liable to use the medicine.

● **Proposal 4:**

Continue assessing the risk of medication error throughout a medicine's life

Medication errors are identified through reports sent to pharmacovigilance systems and to patient safety organisations. These data must then be published in periodic safety update reports (PSUR) (10,11).

When medication errors occur, the initial medication error risk assessment report must be reviewed to improve the risk assessment criteria. Data on overdosing errors and accidental ingestion (involving both active substance and excipients) must be reported without delay in the SPC and public assessment reports (also see proposal 5).

Many major variations (new indication, paediatric extension, line extensions involving new forms or dose strengths, etc.) substantially alter the context in which the drug will be used and consequently the original risk assessment. Drug regulatory agencies should therefore reassess the risk of error associated with its packaging, labelling and associated devices.

Other events in the life of a medicinal product should also prompt re-analysis of both the risk of error and its packaging:

- expanded distribution (when a hospital-only medicine is made available in the ambulatory sector);
- reclassification of a prescription-only medicine as a self-medication product or over-the-counter (OTC) product.

Worksharing procedures to reassess paediatric data on old medicines under Article 45 of the Paediatric Regulation of 2006 are an unmissable opportunity for drug regulatory agencies to ask pharmaceutical companies for practical improvements to their packaging, to improve the safety of all patients (12).

● **Proposal 5:**

Improve information on packaging

The information provided by health authorities for healthcare professionals and patients should be improved:

- Packaging items should be described and instructions for their use provided in the SPC and package leaflet;

- When a new marketing authorisation or major variation is granted, publicly accessible mock-ups of all of the packaging items should be published;
- When a packaging item has caused errors or the potential for error clearly exists, a publicly accessible detailed analysis should be published, linked to or included in the public assessment report (EPAR, national, decentralised or mutual recognition procedure PAR) on the websites of the appropriate medicines agencies;
- When changes are made to any packaging item that could affect how it is used.

● Proposal 6:

Update existing guidelines to improve error prevention

Several existing guidelines are inadequate and need to be refocused, particularly with regard to:

- Recommendations on brand names, which defend trade names at the expense of use of the INN; the focus of these recommendation must be shifted towards patient safety (f) (13);
- Recommendations on the expression of dose strength and concentration in the name of medicinal products exist solely for administrative purposes, to discriminate between the various MA dossiers of the same product line; these recommendations must be revised to prevent errors associated with the coexistence of different dose strengths and concentrations and to help patients and healthcare professionals use medicines correctly (14);
- Recommendations on self-medication products; these recommendations must ensure patient safety by improving the packaging and labelling of self-medication products (g) (15).

● Proposal 7:

Increase the attention given to the prevention of medication errors in all drug regulatory agency activities

In addition to product-specific risks, drug regulatory agencies can avert other sources of error through vigilance and by paying constant attention to the prevention of medication errors, such as foreseeing off-label use.

If the rules on the use of INNs had been applied: the error in the expression of dose for *eribulin* (standardised at 1 mg/2 ml of *eribulin mesilate* instead of *eribulin* base) would have been corrected at the clinical trial stage (16); modified INNs would have been requested for lipid formulations of *amphotericin B* or *daunorubicin* (17); and inappropriate use of brand names in SPCs, such as that of Rasilez^o, would have been avoided; etc.

A priority in the non-prescription or over-the-counter (OTC) sector is to improve the information about pregnancy in the package leaflets of NSAIDs. The data on NSAIDs suggest that their administration during the first trimester of pregnancy increases the risks of miscarriage and malformations. If they are taken after the first trimester, NSAIDs expose the fetus to serious and sometimes fatal cardiovascular and renal risks. However, in some French package leaflets examined in 2011, regardless of dosage form and legal status, NSAIDs were only clearly contraindicated from the sixth month of pregnancy (7).

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Notes:

a- The packaging of medicines of "umbrella" brands are designed to be easily recognised by users as belonging to the same brand. Their graphics make very different medicines look alike, even though they may contain different active substances, with the potential for confusion and medication errors.

b- European and national competent authorities do not publish exhaustive lists of all the medicinal products that are currently authorised in the European Union, nor their summaries of product characteristics (SPCs) and package leaflets. Under these conditions, a comparison with the existing product hardly seems possible.

c- European Commission, European Medicines Agency, Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh), European Directorate for the Quality of Medicines (EDQM) of the Council of Europe.

d- The MA dossier would therefore include a medication errors assessment report, in addition to the clinical assessment report and the safety assessment report.

e- A small device could be included in the box to help patients with limited dexterity remove tablets or capsules from the secure blister pockets.

f- To achieve this, the EMA must:

- publish the list of drug names known to have generated confusion;
- facilitate the reporting by healthcare professionals and patients of drug name-related errors;
- adopt and publish a method for assessing the risk of confusion before marketing authorisation is granted;
- abandon brand name extensions, whereby medicines with different compositions that belong to the same "umbrella" brand have almost the same name (i.e. Nuro something^o) which is confusing;
- adopt stricter standards for the naming of fixed-dose combinations;
- revert to more prudent use of abbreviations and suffixes, which cause confusion;
- involve patients in the search for improvement (ref. 18,19).

g- For self-medication products, it is necessary to:

- stop accepting umbrella brand name extensions, which cause confusion and serious medication errors;
- review the rules on the use of colour on the packaging of medicinal products, taking into account the impact of colour perception defects, which affect a significant proportion of the population;
- organise how information for patients is divided among the package leaflets and the secondary packaging (including the inside of the box) and how the most important information is highlighted; etc. (ref. 15).



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