

2010 drug packaging review: identifying problems to prevent errors



- Prescrire's analyses showed that the quality of drug packaging in 2010 still left much to be desired.

- Potentially dangerous packaging remains a significant problem: unclear labelling is source of medication errors; dosing devices for some psychotropic drugs create a risk of overdose; child-proof caps are often lacking; and too many patient information leaflets are misleading or difficult to understand.

- Everything that is needed for safe drug packaging is available; it is now up to regulatory agencies and drug companies to act responsibly.

- In the meantime, health professionals can help their patients by learning to identify the pitfalls of drug packaging and providing safe information to help prevent medication errors.

Rev Prescrire 2011; 31 (328): 142-145.

In recent years, the beneficial impact of new regulatory measures has emerged in *Prescrire's* annual reviews of drug packaging. These measures include amendments to the European Directive on human medicines (in 2004), that extended the use of international non-proprietary names (INNs) on drug labelling, required the use of Braille on boxes, and provided for user testing of patient information leaflets. The French drug regulatory agency (Afsaps) issued new regulations on the labelling of dangerous injectable drugs.

We also welcomed the decision by several generics manufacturers to highlight the INN on their boxes (1,2). This article reviews the packaging quality of the drugs we analysed in 2010.

Welcome efforts

As in previous years, none of the 300 drug packagings we examined in 2010 included all the important features required for optimal drug use.

Prescrire's Packaging Working Group found too few single-unit blisters or quasi-single-unit blisters (a): examples

include *saxagliptin* (*Prescrire Int* n°113); *prasugrel* (*Rev Prescrire* n°317); and a child-proof blister pack for *fentanyl*, an opiate (*Rev Prescrire* n°319).

Among the packaging examined in 2010, several bottles containing large amounts of dangerous substances were equipped with child-proof caps, including oral *haloperidol* solution (*Rev Prescrire* n° 320).

A few products that require the use of devices for their preparation or administration are sold in a ready-to-use format, with the necessary items included in the packaging. Examples include: *sodium phosphate + bisacodyl* (*Rev Prescrire* n°315); *certolizumab* (*Rev Prescrire* n°325); *CI esterase inhibitor* (*Rev Prescrire* n°321); and *icatibant* (*Prescrire Int* n°110).

In 2010, there were a few improvements in the packaging of existing products. The new oral syringe provided for *Fluanxol*° is now graduated in milligrams of *flupentixol*, a neuroleptic, rather than in the number of drops of solution (*Rev Prescrire* n°318). Similarly, the new syringe provided for *Depakine*° oral solution is now graduated solely in milligrams of *sodium valproate*, rather than in both milligrams and millilitres; like all

dual graduations, this represents a source of confusion (*Rev Prescrire* n°315). The bulk bottles of *doxylamine-Lidene*°, a self-medication product, that lacked a child-proof cap, were replaced by blister packs (*Rev Prescrire* n°315); this was also the case with *indoramin* (*Rev Prescrire* n°318).

Misleading and confusing labelling

In 2010, there remained widespread flaws in drug packaging, along with some unpleasant surprises.

INN not highlighted. The INN (international nonproprietary name) is often not clearly visible, making the drug more difficult to identify, thus increasing the risk of medication errors. In particular, the INN is missing from the front of the box and from the bottle of a solution for inhalation rich in terpene derivatives (*levomenthol + benzoin tincture + eucalyptus tincture + Peru balsam + essential oils of lavender and thyme*) (*Rev Prescrire* n°318).

The INN on the label of *Isofebryl* vitamin C° is printed in thin grey letters 1 mm high, while the "vitamin C" contained in

the brand name is printed in thick orange letters 5 mm high. Yet this product also contains *aspirin* and *paracetamol*.

On the blister packs of *Temeritduo*[°] (*nebivolol* 5 mg + *hydrochlorothiazide* 12.5 mg or 25 mg), the INNs are so small that they can be mistaken for simple underlining of the brand name (*Rev Prescrire* n°320).

Graphic designs of product lines: too easily confused. The use of similar graphics for different dose strengths intended to reinforce the brand image represents another source of confusion. The front sides of the boxes containing the 2 dose strengths of *Temeritduo*[°] are a noteworthy example.

On the front of boxes containing the 4 dose strengths of the *Exforge HCT*[°] product line (*amlodipine* + *valsartan* + *hydrochlorothiazide*), the colour strip intended to differentiate between the dose strengths is largely overshadowed by the other graphics (*Prescrire Int* n°114), thus increasing the risk of medication errors with this combination of three antihypertensive drugs.

The differences between the labelling on blister packs of the various doses of *Exforge HCT*[°] (*aliskiren* + *hydrochlorothiazide* *Rev Prescrire* n°315, 320) and *rufinamide* (*Inovelon*[°]) are also inadequately highlighted (*Rev Prescrire* n°319).

The graphics for the umbrella range *Codotussyl*[°] (*Rev Prescrire* n°317) are another example of poor-quality labelling: a bright fuchsia background and superfluous graphics, such as face of a child or adult (actually resembling an adolescent) in the background. The brand name is far too prominently displayed on products with very different compositions (*acetylcysteine*, *cetylpyridinium*, *lidocaine* or *pholcodine*).

The boxes and bottles of *pholcodine* syrups show a double-ended spoon, with a large spoon at one end (5 ml) and a small one at the other end (2.5 ml). In this illustration, only the large spoon is full, yet the unit dose recommended in the patient information leaflets for children weighing between 20 and 35 kg is 2.5 ml. Community pharmacists should avoid placing this product line on their OTC shelves.

Poor identification of individual blister pockets. Some blister packs examined in 2010 are still associated with a well-known risk: for example, the name and dose of *pramipexole* 0.26 mg (*Rev Prescrire* n°323) span two pre-cut blister pockets.

Blister packs of *DolipraneLib*[°] exhibit a similar flaw (see inset opposite).

Prescrire has been drawing attention to this issue for several years, because of the

risk that patients may inadvertently take a double dose (1,2). Regulatory agencies have thus far failed to take action.

Confusion in expression of concentrations. In 2010, patients remained at risk from the confusing way in which the concentrations of some multidose oral and injectable products were expressed.

One particularly shocking example noted in 2010 concerns two oral solutions of *sodium valproate*, both marketed in France by Sanofi Aventis, that differ in the way in which their concentrations are expressed. The front of the box and bottle of the reference product (*Depakine*[°]) bears the expression "200 mg/ml", while "20%" is used on the only generic version (*Valproate de sodium Winthrop*[°]). This difference can cause confusion if the reference drug is replaced by the generic. This is a significant issue with an antiepileptic drug.

For several years now, the labelling of many injectable products has created a risk of medication errors because of European guidelines requiring the inclusion of the concentration or dose in the name of each proprietary drug. This information may help regulatory agencies to distinguish between different products, but they in no way help health professionals and patients to use drugs correctly (see inset page 165). For example, the SPC for *temsirolimus* (*Prescrire Int* n°111) states that a dose of 25 mg should be injected. The front of the box highlights the administrative information, including the concentration "25 mg/ml". However, the bottle contains 30 mg of the drug in a volume of 1.2 ml, creating a risk of confusion between the total amount of the drug contained in the bottle (30 mg) and the dose to administer (25 mg).

Bottles sold without a box: an exception, or a new trend?

In 2010, 3 drugs marketed in bulk bottles were sold without a box as outer packaging (i.e. secondary packaging): *calcium polystyrene sulfonate* (*Resikali*[°] *Rev Prescrire* n°319); *calcium acetate* (*Phosphosorb*[°] *Rev Prescrire* n°323); and *sevelamer carbonate* (*Renvela*[°] *Rev Prescrire* n°326).

These bottles have a folded sheet attached to their side. The user detaches one end in order to read the information it contains. However, the sheet can be difficult to reattach after several uses, and it sometimes has to be detached completely in order to be read (*Phosphosorb*[°]).

In the case of *Resikali*[°], it is necessary to insert one's fingers into the powder in order to find and pull out the measuring spoon.

Inseparable box/blister pack/leaflet: an interesting new concept

In 2010, *Prescrire*'s Packaging Working Group noted that the box, blister pack and patient information leaflet for *DolipraneLib*[°] *paracetamol* OTC tablets (*Rev Prescrire* n°325) could not be separated.

This design ensures that the patient information leaflet remains on hand throughout the use of the product, and that a blister pack containing another drug cannot accidentally be put in the box of *DolipraneLib*[°] in the family medicine cabinet.

Unfortunately, the printing of the product identifier is systematically spread over 2 blister pockets, each of which contains one 500-mg tablet, a dose that often suffices.

In addition, the information printed on the back of the box does not warn of the risk of serious liver damage when *paracetamol* is taken at the same time as large quantities of alcohol.

This is why *Prescrire* was unable to grant the yearly Packaging Award to this product.

©Prescrire

Boxes protect drugs from light, heat and humidity. They also serve as a container for the patient information leaflet and dosing device. They are, by definition, larger than the bottle, blister pack or syringe they contain, meaning that their labelling can be larger and easier to read. Regulatory agencies must ensure that dangerous substances are not sold without an outer packaging.

Protecting children

Too many dangerous substances are still sold without an adequate child-proof device. This represents a potentially serious problem with OTC products like cough syrups with psychotropic effects, such as *Codotussyl*[°] (a product line described above); and the *Clarix*[°] product line, containing drugs such as *pholcodine* and *pentoxifyverine* (*Prescrire* n°318). ▶▶

.....
a- For further information on the activities of *Prescrire*'s Packaging Working Group, and for explanations on technical terms such as "single-unit blisters" and "quasi single-unit blisters", see reference 2.

FDA: inaccurate dosing devices

In 2009, the US Food and Drug Administration (FDA) examined the dosing devices for 200 oral multidose OTC products intended for pain, cough, allergy and some gastrointestinal disorders in children under 12 years of age (1). The results, published in 2010, are worthy of note.

In line with Prescrire's findings. Only three-quarters of the products examined by the FDA included a dosing device. Four out of five devices were dosage cups, 13.5% were droppers, and only 2.7% were oral syringes, which are more precise than dosage cups and droppers (1).

At least one inconsistency was found between the instructions for use and the graduations on the dosing device for nearly all of the products examined. At least one necessary graduation was missing in nearly one-quarter of cases, while about 8 in 10 devices bore unnecessary graduations. Eleven devices bore atypical units of measurement such as cm³, and 2 different graduated scales were found on half of the dosing devices (1).

In November 2009, the FDA issued a guidance for manufacturers on the design of dosing devices for OTC oral medicines (2). It included the following recommendations: all such products should be sold with a dosing device; the instructions for use should be compatible with the graduations; the highest standards for packaging should become the norm (for example, the capacity of dosing devices should be limited to the maximum recommended dose); and user tests should be conducted.

The FDA's example should be followed in Europe.

©Prescrire

1- Yin SH et al. "Evaluation of consistency in dosing directions and measuring devices for pediatric nonprescription liquid medications" *JAMA* 2010; **304** (23): 2595-2602.

2- Food and Drug Administration "Draft guidance for industry. Dosage delivery devices for OTC liquid drug products" November 2009: 13 pages.

► Bottles of Dolirhume aux huiles essentielles[®], a product rich in terpene derivatives, have aluminium caps that are easy to unscrew. A young child ingesting a large amount would be at risk for the neurological adverse effects of terpene derivatives, such as seizures, hallucinations, and drowsiness (3).

In 2010, a new combination of anti-hypertensive drugs was sold in bulk bottles with easily removable stoppers (*amlodipine + perindopril*, *Rev Prescrire* n°316).

The first *fentanyl* nasal spray (*Prescrire Int* n°110) was marketed in France in plastic boxes designed to make it harder for children to access the multidose bottles. Yet our tests showed they were not difficult to open. In addition, the bottles have a simple push-button spray and are not equipped with a safety cap. However, patients are unlikely to put the bottle back in the inconvenient "tamper-proof" box between uses.

Dosing devices: worrisome trend towards the use of pump bottles

In 2010, few dosing devices were graduated in units corresponding to the weight of drug. Most were graduated in millilitres, requiring the user to calculate the weight equivalent, another potential source of error. Worse yet, the dosing device for *levetiracetam*, an antiepileptic drug (*Rev Prescrire* n° 321), is now graduated in ml whereas it used to be graduated in mg (see also *Rev Prescrire* n°327).

The use of droppers, which are obsolete and imprecise, is especially dangerous with psychotropic drugs such as *haloperidol* and *escitalopram* (*Rev Prescrire* n°319).

In 2010, oral *memantine* (*Rev Prescrire* n°323), previously available in dropper bottles, was sold instead in spray bottles equipped with a metered pump that has to be primed and has no refractory period (minimum time between 2 puffs). One push delivers 5 mg of *memantine*, i.e. 10 times more than a drop with the use of the old bottles. As expected, soon after the new packaging of the oral form was released, errors, including cases of overdose, occurred. In late 2010, the company made the labelling clearer but did not change the dosing device.

Instanyl[®] is also delivered via a spray pump that needs to be primed and has no refractory period. The company that markets it has announced it will provide a single-dose safety bottle. In the meantime, there remains a risk of potentially fatal overdose (see above).

Patient information leaflets: too often inadequate

Although readability tests of patient information leaflets have led to improvements, too many leaflets are still misleading or difficult to understand (1,2).

Leaflets for OTC cough syrups examined in 2010 (the *Codotussyl[®]* and *Clarix[®]* product lines, for example) do not explain the natural course of normal, mild cough, or (adequately) deal with non-drug options. Yet antitussives are barely, if at all, more effective than simply sucking a sweet or drinking liquids (4,5). This information is not specified in the patient leaflets.

Patient leaflets for some OTC NSAIDs are incomplete or ambiguous in terms of the risks to the unborn child in pregnant women. The leaflet for *ibuprofen* tablets (*Nurofenem[®]* *Rev Prescrire* n°320) does not clearly mention that NSAIDs are contraindicated during the first trimester of pregnancy, even though the data point to an increased risk of miscarriage (6). The leaflet simply states (our translation): "during the first trimester of pregnancy (...), your physician may, if necessary, prescribe this drug".

A greater problem exists with the leaflet for *VoltarenPlast[®]* *diclofenac* plasters (*Rev Prescrire* n°320) that states (our translation): "during the first 6 months of pregnancy, *VoltarenPlast[®]* (...) may only be used if recommended by your physician". This is particularly dangerous: NSAID use during the second trimester can cause severe renal and cardiovascular disorders in the foetus (7).

What are patients likely to make of these ambiguous statements? Why do the leaflets for all NSAIDs not simply contraindicate their use in self-medication throughout pregnancy (8), as in some direct-to-consumer advertisements?

Some injectable drugs must be prepared and administered by a healthcare professional, but not all the relevant leaflets contain complete instructions (e.g. *tocilizumab*, *Rev Prescrire* n°320). This information is sometimes contained in detailed brochures provided to health professionals by the company. These brochures should be read with a critical eye. It would be simpler if the boxes contained the information required by all those concerned.

In practice

Overall, the poor quality of drug packaging continues to undermine patient safety (see our comment opposite).

While waiting for drug companies and regulatory agencies to take this issue seriously, health professionals seeking



to improve patient care can help by learning to assess the quality of packaging items, reporting poorly designed drug packaging, and providing information and advice to their patients, thus reducing the risk of medication errors.

©Prescrire

Selected references from Prescrire's literature search.

- 1- Prescrire Editorial Staff "Drug packaging in 2009: a few advances" *Prescrire Int* 2010; **19** (107): 135-137.
- 2- Prescrire Editorial Staff "Packaging of pharmaceuticals: still too many dangers but several encouraging initiatives" *Prescrire Int* 2007; **16** (89): 126.
- 3- Afssaps "Commission nationale de Pharmacovigilance - Compte rendu de la réunion du mardi 25 mai 2010" 6 July 2010: 6-14.
- 4- Prescrire Rédaction "Toux gênantes" *Rev Prescrire* 2008; **28** (299): 676-677.
- 5- Prescrire Rédaction "Médicaments de la toux et rhume: effets indésirables trop graves face à des troubles bénins" *Rev Prescrire* 2009; **29** (312): 751-753.
- 6- Prescrire Rédaction "AINS topiques: gare en cas de grossesse" *Rev Prescrire* 2008; **28** (299): 664.
- 7- Prescrire Rédaction "Gare aux AINS en deuxième partie de grossesse" *Rev Prescrire* 2007; **26** (270): 188-191.
- 8- Prescrire Rédaction "Infos-patients - Pas d'anti-inflammatoire pendant la grossesse" www.prescrire.org: 1 page.

Regulatory agencies and companies must take packaging more seriously

Everything that is needed to produce safe and convenient drug packaging is already available on the market (see opposite), yet the quality of most packaging remains mediocre. As a result, some products carry a risk of potentially dangerous medication errors.

Guidelines needed. Guidelines are needed for packaging safety, including: quality criteria for unit-dose packaging; the design of dosing devices; safety guidelines for dangerous substances; careful use of colour on the labelling in order to distinguish between different dose strengths belonging to the same product line; specific recommendations for paediatric drug packaging; and key information for patients, according to the nature of the medication, its indications, route of administration, pharmaceutical form, and devices for preparation and administration.

Existing guidelines tend to focus on administrative requirements and cost rather than on the quality of patient care. For example, European recommendations on the expression of drug concentrations and dose strengths exist solely for administrative purposes, not to

help health professionals and patients use drugs correctly (1).

More stringent controls. Some drugs with dangerous packaging still reach the market despite controls put in place by European or national regulatory authorities and pharmacovigilance committees. The French Transparency committee is supposed to weigh the advantages and disadvantages of new drugs relative to existing products; this includes the packaging. Ineffective controls create an unacceptable risk of confusion and medication errors in practice.

Making drug packaging safer and more convenient to use is a means of improving the quality of health care. Regulatory agencies and drug companies must take this issue more seriously.

©Prescrire

Rev Prescrire 2011; **31** (328): 145.

- 1- European Medicines Agency "QRD Recommendations on the expression of strength in the name of centrally authorised human medicinal products" 18 November 2009 + "Submission of comments - Comments from International Medication Safety Network" 28 May 2009: 5 + 9 pages.



Coming soon...

NEW PRODUCTS

- Fingolimod
- Sublingual 5-grass pollen mix
- Atazanavir in children
- Dexamethasone intravitreal implant

ADVERSE EFFECTS

- Fatal adverse events during hospital stays
- Tamoxifen and CYP 2D6 inhibitors: caution
- Tadalafil: visual and auditory disorders

REVIEWS

- Seasonal influenza vaccination of the elderly
- Retinal vein occlusion
- Ivabradine in heart failure: no better than optimised beta-blocker therapy

Outlook

- HIV infected patients: victims of the financial crisis
- Measuring survival time
- Astellas' lawsuit against Prescrire