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Drug packaging in 2014: Authorities should direct more efforts towards medication safety

Abstract

● **In 2014, *Prescrire* examined the packaging quality of about 250 drugs. A few advances stand out, mainly involving recent drugs, but on the whole, the situation is worrisome in terms of medication safety.**

● **Although pharmaceutical companies and drug regulatory agencies seem to be taking more account of the risk of accidental poisoning in children, the level of protection remains low overall in the absence of stringent measures on the part of the authorities.**

● **New drugs too often have poor-quality or even dangerous packaging at the time of their market introduction. And the packaging quality of older drugs is disturbing. Pharmaceutical companies no longer invest in the packaging of these products, and agencies often fail to take advantage of the opportunities provided by their reassessment to improve the situation.**

● **The inappropriate labelling of certain injectable drugs remains a source of medication errors, sometimes resulting in very serious consequences.**

● **In 2014, signs of progress in the packaging of several drugs show that its role in medication safety is better appreciated. But the persistence of dangers in the pharmaceuticals market, created by "unfinished", overly complex or poor-quality packaging, raises the question of the responsibility of pharmaceutical companies and agencies for past and present accidents.**

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In 2014, *Prescrire* examined the packaging quality of about 250 drugs available on the French market, as part of our procedure for evaluating new products and changes to existing products (new indications, line extensions, etc.).

The role of packaging in medication safety often appears to be underestimated, if not ignored (1). Marketing objectives or efforts to minimise manufacturing costs often undermine the quality of drug packaging and sometimes generate risks. Although substandard packaging is still all too common, many satisfactory solutions exist, and every year *Prescrire* finds that some have been incorporated into the products we examine. In 2014, some signs of progress stood out from a situation that, on the whole, was worrisome.

INNs: slowly becoming more legible

Good-quality labelling must help patients and healthcare professionals remember the real name of their drugs, i.e. the international nonproprietary name (INN). The INN is often difficult to read on boxes or primary (immediate) packaging (blister packs, bottles, single-dose containers, etc.), and sometimes impossible to read once blister pockets have been detached from a multi-unit pack to prepare a treatment.

Among the packaging examined by *Prescrire* in 2014, the INN was absent from the single-dose containers of three types of eye drops and a blister pack containing tablets (an omission that earned the companies concerned a Yellow Card in the annual *Prescrire* Packaging Awards, see *Prescrire International* issue n° 158, p. 77). The INN was poorly legible (characters too small, insufficient contrast with the background) on the box or blister pack of a number of other products, such as *propylthiouracil* (Propylex°), oral *piribedil* (Trivastal°), and the *diclofenac* product FlectorEffigel°.

In contrast, some companies have chosen to prominently display INNs on their boxes in recent years. INNs are still often overshadowed by the brand name, but they are clearly displayed in bold, legible characters, sometimes in a different colour from the rest of the information on the box. Notable examples in 2014 included: *brimonidine* cutaneous gel (Mirvaso°); *pomalidomide* (Imnovid°); *sofosbuvir* (Sovaldi°); and *vemurafenib* (Zelboraf°). The INN is even more legible when pharmaceutical companies decide not to use an invented name, include the INN in the brand name and display it prominently on the box: examples include Colchicine Opocalcium°, Baclofène Zentiva° and Néfopam Mylan° (*baclofène* and *néfopam* are the French for the INNs *baclofen* and *nefopam*).

Children and the risk of poisoning: solutions for avoiding accidents

One important aspect of a drug's packaging is that it must protect children from the risk of accidental ingestion. Child-resistant packaging that incorporates safety features to prevent or delay access to a dangerous drug should be the norm. Simple solutions exist but are neither adopted by pharmaceutical companies nor required by drug regulatory agencies.

In 2014, ten products received a Red Card in the *Prescrire* Packaging Awards because they lacked a child-proof cap (see *Prescrire International* issue n° 158, p. 76). Most of these products contain large quantities of a psychotropic antiepileptic, neuroleptic or opioid drug, or sometimes a high concentration of alcohol, all of which could cause a serious overdose if ingested by a child.

In 2014, in France, a cutaneous foam containing 5% *minoxidil* was marketed with a lockable cap that is difficult to remove. But this advance stands in contrast to all the bottles of *minoxidil* solution available in France that lack a child-proof cap.

Another positive example: in response to serious disorders reported following accidental ingestion of *brimonidine* cutaneous gel (Mirvaso°) by children during its clinical development, the tube containing the gel was marketed with a child-proof cap (2). This is the first time *Prescrire* has examined a child-proof cap on a tube of a drug intended for topical application, and it appeared effective in our tests.

Child-resistant blister pack or bottle: drug companies get to choose? The safety of packaging for tablets and capsules should also be a priority for drug regulatory agencies in 2015. Several new cytotoxic drugs are marketed in bulk bottles fitted with a child-proof cap. But child-resistant blister packs, in which each blister pocket is covered by a film that is difficult for young children to peel off, are a better solution.

The most important advantage of child-resistant blister packs compared with bulk bottles is that doses remain identifiable even when separated from the pack. Child-resistant blister packs are too rare: in 2014, we noted that the *fentanyl* product Recivit° had been packaged in this way. But most drugs supplied in blister packs, including cytotoxic agents, do not have child-resistant packaging.

There are child-resistant packaging solutions on the market, and others have been proposed (**a**). Have drug regulatory agencies identified and tested them, without waiting for pharmaceutical companies to adopt them voluntarily?

Old drugs: apathy = danger

Reassessments of older drugs, initiated by the French Health Products Agency (ANSM), have had little impact on packaging.

In 2014, following a European reassessment, *metoclopramide* oral solution (Primpéran°) was re-authorised for children. Previously, no dosing device had been supplied in the box. A syringe graduated in milligrams has been added, but the bottle remains unsafe because it still lacks a child-proof cap.

In 2014, the company that markets Kaneuron° (*phenobarbital*) improved the oral delivery syringe provided with this antiepileptic drug. The syringe is no longer marked with two different types of graduations, which was a source of confusion and dosing errors. But two different dosing devices (a syringe and a dropper) are provided in the box, which the patient leaflet does little to explain. In 2013, the ANSM advised against supplying different types of dosing devices in the same box (**b**)(3). Finally, the bottle containing Kaneuron° still lacks a child-proof cap.

Labelling of oral potassium: ANSM action required. *Potassium* overdose can cause serious and even fatal cardiac disorders. In 2011, the ANSM reported a death associated with the use of injectable *potassium* (4). In 2002, the United Kingdom withdrew concentrated injectable *potassium* solutions from all hospital wards apart from critical care units and emergency departments (*Rev Prescrire* n° 244). In France, the ANSM imposed high-quality labelling for injectable *potassium* (*Rev Prescrire* n° 290).

But in 2014, *Prescrire*'s reviews of Diffu K° and Potassium Richard° syrup showed that oral *potassium* drugs are particularly badly packaged. Diffu K° has been marketed in France for many years, often referred to as Diffu K° 600, a name that is still used in some prescribing software. The number 600 corresponds to the mass in milligrams of microencapsulated *potassium chloride* (including the mass of the coating excipients).

But in June 2013, the quantity of *potassium* element was added to the box: 313 mg. *Potassium chloride* 600 mg is still printed on the blister packs. Yet according to the French summary of product characteristics (SPC), *potassium chloride* (KCl) accounts for 80% to 90% of microencapsulated KCl. And when users consult the ANSM website for information about this drug, the page shown states that each capsule contains 480 mg to 540 mg of KCl. It is curious that this range should translate to the single quantity of 313 mg of *potassium* element, shown on the box. The dose is expressed in milliequivalents (8 mEq) on other packaging items, because this unit is used in wards that administer injectable *potassium*. The labelling of the *potassium* content of Diffu K° is complex and could lead to confusion.

We also examined Potassium Richard° syrup in 2014. It is supplied in multi-dose bottles but lacks a dosing device. Users therefore have to measure doses with a household spoon, even though this is well known to be inaccurate. And the bottle lacks a child-proof cap. Adequately labelled single-unit sachets are also authorised under the same name.

Injectable drugs: too many preparation steps, and dangerous labelling

Most of the newly marketed single-dose injectable drugs examined in 2014 are offered in a suitable packaging format: a pre-filled syringe protected inside a sealed tray (**c**).

But many of the injectable drugs supplied in vials that we examined this year burden healthcare professionals with: several steps for reconstitution or dilution; confusing labelling, on which the strength is expressed in a variety of different ways; and overfills that create a risk of sometimes serious overdose. The most dangerous example examined in 2014 is *cabazitaxel* (Jevtana°) (*Rev Prescrire* n° 372). ▶▶

a- For example, one company proposes packaging (Locked4kids°) that appears to make it difficult for young children to remove blister packs from their outer packaging. The blister packs are stacked inside a tray that slides into the box like a drawer. Once inside its box, the tray is locked in position. The tray is removed from the box by simultaneously pressing two points on the box (http://www.youtube.com/watch?v= 8dlNtaq0yuI).

b- Prescrire participated in the public consultation on ANSM's draft recommendations, some of which would improve patient safety. As of 5 January 2015, the final recommendations have not yet been published on the ANSM website.

c- Influvac°, one of the influenza vaccines marketed in France for the 2014-2015 season, has extremely pared-down packaging. The only protection for the pre-filled syringe is a cardboard box, rather than a sealed tray.

Jevtana°: at least 3 deaths attributed to overdose. Each box of Jevtana° contains two vials: one containing *cabazitaxel* concentrate and one containing solvent with which to dilute the concentrate.

Both vials contain an overfill to compensate for losses during preparation. The prepared solution has a concentration of 10 mg/ml, a volume of 7.3 ml and contains a total of 73.2 mg of *cabazitaxel*.

However, for what appear to be administrative reasons, the dose strength displayed on the box and label is "Jevtana° 60 mg", which corresponds to the quantity of *cabazitaxel* present in just 6 ml of the prepared solution. Difficulty understanding the preparation of the final diluted solution, with various volumes and quantities marked on the *cabazitaxel* vial and the solvent vial, has led several healthcare professionals to prepare solutions that were too concentrated, resulting in overdose. There have been 14 deaths, 3 of which were directly attributed to errors. The labelling has since been improved, but some ambiguity remains.

Address ambiguity over doses of injectable drugs. The dangers of confusing one way of expressing the quantity with another when preparing injectable drugs are not new. For example, in 2012, a clarification had to be added to the European SPC for Halaven° (*eribulin*), due to confusion between the two ways in which its strength was expressed, sometimes referring to the quantity of *eribulin* salt and other times to *eribulin* base.

In 2014, we identified other examples of injectable drugs where we considered the preparation procedure too complex: the *dexrazoxane* product Cyrdanax°, *pixantrone* (Pixuvri°), *trastuzumab emtansine* (Kadcyla°), and *tocilizumab* (Roactemra°).

Anakinra (Kineret°) was authorised for children in November 2013. According to the company, it will be marketed in a new format in 2015 in France, including a specific syringe with graduations indicating the correct dose based on the child's body weight. In the meantime, the syringe designed for adults is provided in the box; it has no graduations at all, creating a risk of overdose if the drug is used in children.

The packaging of a number of drugs for intravitreal injection requires improvement such as *aflibercept* (Eylea°) and *ocriplasmin* (Jetrea°) in overfilled vials. More suitable packaging should have been designed prior to market introduction, by reducing the overfill volumes and providing a pre-filled syringe as an alternative to the vial. In summary, these drugs appear to have been placed on the market with "unfinished" packaging.

Patient leaflets must be clear and informative

The purpose of the patient leaflet is to provide patients with information about their medication. It must be updated as more knowledge about the drug is acquired.

According to the regulations, readability testing among target patient groups is supposed to make patient leaflets clearer, easier to use and more informative.

NSAID patient leaflets and pregnancy: conservatism on the part of the ANSM, minimal information. In 2014, *Prescrire* confirmed its position on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy.

In the second trimester of pregnancy, serious fetotoxic effects occur even after brief 3-day exposure (*Rev Prescrire* n° 358). Yet patient leaflets only contraindicate NSAIDs from the 6th month of pregnancy. It is much better to avoid NSAIDs throughout the second trimester, until this 6-month cut-off has been shown to be relevant.

NSAIDs should also be avoided during the first trimester of pregnancy, mainly due to the risk of spontaneous abortion and malformations (5). In the event of regular fetal exposure, anomaly scans to monitor the unborn child's heart are advisable, due to concerns over the risk of cardiac malformations. NSAID patient leaflets should reflect the reality of such a clinical situation. Yet most of the patient leaflets examined in 2014, even for NSAIDs intended for self-medication, lacked any reasoned reservations about the use of this type of drug during the first trimester of pregnancy, apart from the need for medical advice.

Clear, informative patient leaflets do exist however. In recent years, several patient leaflets reflect the efforts made to highlight the most serious risks of the drug in question. They are presented in a clear and detailed manner at the top of the section, separate from the sometimes long and off-putting list of adverse effects classified by frequency and organ. In 2014, the patient leaflet for the cytotoxic drug *aflibercept* (Zaltrap°) appeared particularly well designed in this regard (6). This drug is for hospital use, so may not be given to patients, but they can find it on the internet.

Other positive examples of informative patient leaflets were noted for a four-drug combination containing *cobicistat + elvitegravir + emtricitabine + tenofovir* (Stribild°), and for *dolutegravir* (Tivicay°) (7,8).

These advances corroborate the trend towards better quality patient leaflets for drugs authorised through European marketing authorisation procedures, where readability testing conducted among target patient groups appears to be having more impact.

Motivate companies and regulators to take action by reporting errors, dangers and accidents

The progress observed in packaging in 2014 and in previous years shows that regulators have realised the importance of packaging in medication safety. But the standard demanded is too low, and too many new drugs arrive on the market in a form and in packaging that leave much to be desired. And insufficient resources and attention are devoted to improving the poor packaging of numerous older drugs.

The most effective way for healthcare professionals and patients to combat this problem is by reporting errors and dangers, including those that had no clinical impact. These reports serve to remind pharmaceutical companies and drug regulatory agencies of their responsibility for accidents attributed to packaging and for identified dangers in drugs they have placed on the market, and motivate them to take action to improve medication safety.

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Drug packaging in 2013: small changes would reap big benefits" *Prescrire Int* 2014; **23** (149): 136-139.

2- EMA-CHMP "Public assessment report for Mirvaso. EMEA/H/C/002642" 19 December 2013: 107 pages.

3- ANSM "Projet: recommandations relatives aux dispositifs d'administration des spécialités sous forme buvable en multidoses (hors produits homéopathiques)" 31 July 2013: 2 pages.

4- ANSM "Erreur lors de l'administration du chlorure de potassium injectable" 2011: 2 pages.

5- Prescrire Rédaction "À écarter en cas de grossesse: les anti-inflammatoires non stéroïdiens (AINS)" *Rev Prescrire* 2013; **33** (358): 604-605.

6- European Commission "Package leaflet-Zaltrap" 27 June 2014: 11 pages.

7- European Commission "Package leaflet-Stribild" 9 September 2014: 12 pages.

8- European Commission "Package leaflet-Tivicay" 16 January 2014: 12 pages.