Drug packaging in 2017: quality is improving, but many dangers remain

ABSTRACT

● ***Prescrire*** **examined the packaging quality of 318 products in 2017. There is a striking contrast between the advances observed, the lax attitude of drug regulatory agencies, and the failure of many pharmaceutical companies to incorporate these advances into their own products, especially: safer labelling, more accurate dosing devices, child-proof caps, and package leaflets that help protect patients.**

● **The progress observed is mainly due to advances in regulatory requirements and the publication of guidelines by health authorities to increase patient safety. But pharmaceutical companies and regulatory agencies often fail to apply these measures, which owe much to pressure from civil society.**

● **In practice, this means that in 2017, as in previous years, we found many drugs marketed in bulk bottles rather than in child-proof unit-dose blister packs, a safer and more convenient option; bottles without a child-proof cap; and insufficient prominence given to international nonproprietary names on boxes or labelling. Healthcare professionals therefore need to be extremely vigilant in order to identify these dangers, warn patients about them, and report them to health authorities.**

Rev Prescrire **2018; 38 (414): 294-299**

The objectives of *Prescrire*'s annual drug packaging reviews are to inform healthcare professionals of the main dangers posed by the packaging of drugs currently on the market, with the goal of preventing medication errors; and to promote the quality standards that pharmaceutical packaging should meet to maximise patient safety. They are also aimed at drug companies and regulatory agencies, in order to raise awareness of the many dangers and improve medication safety (1).

Positive developments, but still many dangers

Over the past 37 years, *Prescrire* has examined the packaging of about 7000 drugs. Various advances have been observed during this time: greater consideration is given to the risk of medication errors posed by dangerous packaging; more medicines are clearly labelled with the drug's true name, i.e. the international nonproprietary name (INN); the quality of dosing devices has improved; and more bottles are equipped with a child-proof cap. In late 2017, the French Health Products Agency (ANSM) recommended unit-dose blisters as the best method of protecting and identifying tablets and capsules; and in early 2018, it called for an end to umbrella brands (2-4). But progress is slow. The packaging of many drugs is still unsuited to the various situations in which they will be used, and exposes patients to dangers rather than ensuring their safety.

This review cites various examples of packaging advances or dangers among the 318 drugs *Prescrire* examined in 2017.

Some advances: legible INNs, prominently displayed dose strengths, perforated unit-dose blisters. Each year, the INN is clearly legible on the packaging of more medicines. Examples from 2017 include Cresemba° (*isavuconazole*), Ibrance° (*palbociclib*), and Zavicefta° (*ceftazidime + avibactam*). As a result, the active ingredient or ingredients contained in these medicines are easily identifiable.

Perforated unit-dose blister packs are the best type of packaging for tablets or capsules. Each detachable dosage unit remains fully labelled with its INN, dose strength, batch number and expiry date until administration, eliminating the need for healthcare professionals to repackage and relabel them.

Although perforated unit-dose blister packs are much rarer in the community than in hospitals, their use is becoming more widespread in France, for example: Dépamide° (*valpromide*), Dépakote° (*valproate semisodium*), Tagrisso° (*osimertinib*), Mysildecard° (*sildenafil*), and Kalydeco° (*ivacaftor*). The first generic version of the *emtricitabine + tenofovir disoproxil* combination to be made available in France was marketed by Mylan in perforated unit-dose blisters. This packaging represented a clear improvement over the bulk bottles of the originator drug Truvada° and earned a 2017 Prescrire Packaging Award.

Poorly legible INNs and dose strengths. The absence or illegibility of the INN on some packaging reflects the lack of attention on the part of pharmaceutical companies and health authorities to the importance of identifying the active ingredients. It remains a relatively common practice, for example: the blister pack of Bactérix° lacks the INN *nifuroxazide*, and the front of the box of Nausicalm° syrup lacks the INN *dimenhydrinate*. The INN is present but difficult to read on various products: Ponstyl° (*mefenamic acid*); Zimino° (*levosimendan*), the Vogalène°/Vogalib° range (*metopimazine*); Drill Rhume° (*chlorphenamine + paracetamol*); and Biocalyptol° (*pholcodine*). The INNs are particularly small and indistinct due to insufficient contrast with the background on the blister packs of Delprim°

(*trimethoprim*) and the bottle of Lysopaïne° mouth spray (*ambroxol*).

The labelling of Ferrostrane° syrup (*sodium feredetate*) poses a risk to users because they are obliged to calculate the quantity in mg of elemental *iron* per ml based on the uninformative statements "0.68%" or "0.68 g per 100 ml".

A common practice in the labelling of fixed-dose combinations, such as Skudexum° (*tramadol* + *dexketoprofen*), is to display the INNs on the packaging as "*tramadol/dexketoprofen*" and the dose strength as "75 mg/25 mg". It would improve the clarity of labelling if the quantity of each drug were indicated immediately after its INN, i.e. "*tramadol* 75 mg" and "*dexketoprofen* 25 mg".

In France, the ANSM has a major role to play in demanding that pharmaceutical companies apply the safest labelling practices set out in European regulations and guidelines. Substandard labelling has been all too common in France in recent decades, but in late 2017, the ANSM finally proposed guidelines to ensure that drug packaging is clearly labelled with the information needed for patient safety, in particular the INN (2,3).

Bulk bottles: unsuitable for tablets or capsules. Tablets and capsules are sometimes packaged loose in bottles. To prepare a dose, the user must pick one tablet or capsule out of the bottle or pour some into a cupped hand. Some medications, such as cytotoxic drugs, are dangerous to handle. After the drug is removed from the bottle, it is no longer protected and is susceptible to degradation. And it can then only be identified by its appearance and any markings on its surface. In hospitals and other institutions that operate a patient-specific unit-dose drug distribution system, healthcare professionals have to repackage and relabel tablets and capsules supplied in bulk bottles. Both of these procedures can give rise to medication errors.

As in previous years, several new drugs we examined in 2017 were marketed in bulk bottles: Cosimprel° (*bisoprolol* + *perindopril*), Epclusa° (*sofosbuvir* + *velpatasvir*), Résitune° (*acetylsalicylic acid*), Velphoro° (*sucroferric oxyhydroxide*), and Wakix° (*pitolisant*). Other drugs continue to be marketed in bulk bottles, such as Ascofer° (*ferrous ascorbate*), Ferriprox° (*deferiprone*), Kuvan° (*sapropterin*), Dépakine Chrono° and others (*valproic acid*), Mestinon° 60 mg (*pyridostigmine*), Orfadin° (*nitisinone*), Truvada° (*emtricitabine* + *tenofovir disoproxil*), and Zytiga° 250 mg (*abiraterone*). The oral powders, Fumafer° (*ferrous fumarate*) and Kayexalate° (*sodium polystyrene sulfonate*), are also supplied in bulk containers. Dose preparation would be easier and more accurate if they were supplied in a range of single-dose sachets, containing the quantity required per dose and covering all the recommended doses.

Non-unit-dose blisters: problem with identification of each unit. A common packaging flaw is to present multiple dosage units in a blister pack without fully labelling each blister pocket. The required information is often printed diagonally and straddles several dosage units. This type of packaging is often encountered in ambulatory care, and the problem is often compounded by other flaws, such as the use of small, indistinct lettering for INNs. As a result, the overall quality of their labelling is very poor; examples include Drill Rhume° (*chlorphenamine* + *paracetamol*), Nausicalm° capsules (*dimenhydrinate*), Vogalib°/Vogalène Lyoc° (*metopimazine*) and Delprim° (*trimethoprim*).

Non-unit-dose blisters prevent advance preparation of single doses that are clearly identified and protected by their original packaging. Healthcare professionals or caregivers of patients at home sometimes need to detach individual doses from these blister packs, but once detached, there is a high probability that the INN and dose strength will be truncated or missing entirely. In institutions that operate a patient-specific unit-dose drug distribution system, this type of packaging obliges healthcare professionals to repackage and relabel each dose. Both practices carry a risk of error.

Wallet-style blister packs: convenient in the community, unsuitable for hospitals. Some boxes of drugs contain trifold wallets made of two layers of cardboard. The left-hand section generally displays information about the drug (INN, dose strength, brand name). It sometimes has a slot for inserting the patient leaflet. The tablets or capsules are contained in blister packs, mounted between the two layers of the other two sections. The blister pockets protrude through holes, allowing access to the drug.

These wallets are particularly well-suited to drugs with complex dosing schedules (weekly, progressive). For example, the wallet format of Emend° (*aprepitant*) designed for the start of treatment has one 125-mg capsule in the central section, labelled "day 1", and two 80-mg capsules in the right-hand section, labelled "day 2" and "day 3". This solution appears clear and provides an extra layer of safety for patients in an ambulatory setting.

Hospitals and other institutions can purchase Emend° in a unit-dose format, but several drugs are only marketed in wallets, making them unsuitable for patient-specific unit-dose drug distribution, for example: Aubagio° (*teriflunomide*), Jinarc° (*tolvaptan*) and Zepatier° (*elbasvir* + *grazoprevir*) (**a**).

Oral liquid preparations, dosing devices: ANSM guidelines are too rarely applied

In 2016, the ANSM published a guideline for the pharmaceutical industry aimed at improving the quality of dosing devices. Our examination of packaging quality in 2017 shows that drug companies rarely followed this guideline (1).

Yet again, many flaws were observed. For example, no dosing device was supplied with the syrups Codédrill° (*codeine*), Drill Maux de Gorge° (*alfa-amylase*) or Hexapneumine Adultes° (*biclotymol*

+ *chlorphenamine* + *pholcodine*). And far too many oral liquid drugs were supplied with a plastic spoon or measuring cup, which are inaccurate dosing devices, for example Fumafer° (*ferrous fumarate*), Kayexalate° (*sodium polystyrene sulfonate*), and most bottles containing *pholcodine, oxomemazine* or *carbocisteine*.

Pharmaceutical forms that require complex preparation, in particular oral liquid drugs for children. It is better to choose drugs that are ready to use or whose dosage form and packaging minimise the number of preparation and administration steps. The autoinjector pens Metoject° or Nordimet° constituted an advance in 2017 for patients taking *methotrexate*, as they are safer than multidose bottles and more convenient than pre-filled syringes.

At the European level, a tendency was observed to develop paediatric drugs with very complex preparation methods and packaging. They are powders for oral suspension requiring several preparation steps: users have to measure a specific volume of water, prepare a suspension of the powder in this water, measure the volume of suspension to administer (without confusing the quantity prescribed in milligrams with the quantity to measure in millilitres), and then dispose of the unused surplus suspension. Examples include the paediatric forms of Emend° (*aprepitant*), Isentress° (*raltegravir*), Norvir° (*ritonavir*) and Kuvan° (*sapropterin*). Complex preparation methods increase the risk of dosing errors and often require the intervention of a health professional to prepare the drug.

Little protection for children against the risk of poisoning

One key measure to protect children is to equip multidose bottles with a child-proof cap, as is the case for Likozam° (*clobazam*), Zyrtec° (*cetirizine*), Aerius° (*desloratadine*) and Clarityne° (*loratadine*). Stoppers that incorporate a measuring pipette or dropper should also be child-proof, as is the case with Abilify° (*aripiprazole*). But many drugs still have no child-proofing.

Unacceptable dangers. In 2017, as in previous years, some new drugs were authorised in bottles without a child-proof cap: Activox Rhume Pélargonium° (*Pelargonium root extract*) and Cosimprel° (*bisoprolol* + *perindopril*). Some of the child-proof caps we tested were too easy to open, such as the one on the bottle of Résitune° (*acetylsalicylic acid*).

Many older drugs continue to pose a danger to children. Ferrostrane° syrup (*sodium feredetate*) has been marketed in France for five decades in a multidose bottle with no child-proof cap. The company has said it will add a child-proof cap in 2018.

Among the *pholcodine* syrups examined in 2017 (Biocalyptol°, Dimétane°, Hexapneumine°, etc.), only one bottle had a child-proof cap (Poléry Enfants°). The boxes and bottles of the multidose powder Fumafer° (*ferrous fumarate*), which looks like chocolate powder, and those of the vanilla-flavoured powder Kayexalate° (*sodium polystyrene sulfonate*), have no child-proofing. And an overdose of any of these drugs would be dangerous for a child.

Protecting blister packs. Blister packs delay a child's access to a large quantity of tablets or capsules. But when ingestion of just a few tablets could kill a child, as is the case with *colchicine*, it is irresponsible not to add another layer of safety. An ideal choice in this situation is to cover the blister pack with a child-proof film, as has been done for the opioid Méthadone AP-HP°, even if it means providing a tool in the box to help adults remove the tablets. Another option is to have a safety catch on the box to prevent children from removing the blister pack.

Herbal medicines: insufficiently informative packaging

In 2017, we examined the packaging of four herbal medicines. *Pelargonium root extract* (Activox Rhume Pélargonium°, Belivair Rhume Pélargonium°) can provoke gastrointestinal disorders and hypersensitivity reactions, and hepatic disorders have been reported. Dry extract of *ivy* leaves (Herbion Expectorant Lierre°) can provoke gastrointestinal disorders and allergic reactions. The packaging of all these drugs, as well as that of Nirva°, containing dry extract of *passion flower*, is insufficiently informative. Sometimes the packaging of herbal medicines is dangerous: useful information overshadowed by the brand name, scientific names of the active ingredients that are difficult to read, poorly-labelled non-unit-dose blisters packs, inaccurate dosing devices, lack of a child-proof cap, and patient leaflets that are difficult to understand or that omit important information.

We also found that the French summaries of product characteristics (SPCs) and patient leaflets for several herbal medicines (e.g. Activox Rhume Pélargonium° and Nirva°) are not published on the ANSM website or the French publicly accessible drug database (http://base-donnees-publique.medicaments.gouv.fr/).

Packaging and teratogenicity: an important development in 2017

The serious harms to which the unborn child is exposed when drugs are taken during pregnancy are often only recognised after years or even decades of use.

a- Some blisters mounted in wallet-style secondary packaging display information about the drug on the wallet, but not on the blister itself (e.g. Emend° aprepitant). If the blister has to be removed from the wallet in order to detach a blister pocket to prepare a patient's treatment, the drug is no longer identifiable unless relabelled.

A pictogram on most boxes. To draw attention to these dangers, in 2017, a French support group for parents of children affected by fetal anticonvulsant syndrome (APESAC), convinced the ANSM to add a pictogram to boxes of drugs containing *valproic acid* or its derivatives, a measure that was subsequently extended to all teratogenic or fetotoxic drugs marketed in France (5).

Since the analysis we published in late 2017, we have observed a number of inconsistencies while monitoring the implementation of this measure. One example concerns two drugs containing *ibuprofen*. *Prescrire* has often highlighted the harms associated with taking nonsteroidal anti-inflammatory drugs (NSAIDs) at any stage of pregnancy (6). On the box of Spifen°, which we examined in December 2017, the statement accompanying the "prohibited" pictogram (a ring with a diagonal line through it) correctly applies to all stages of pregnancy and is consistent with the risks stated in the pregnancy section of its SPC, which mentions harms from the first trimester onwards. But the statement next to the "prohibited" pictogram on boxes of Ibuprofène Sandoz°, which we examined in November 2017, is "*do not use in pregnant women from the 6th month of pregnancy*", because it is based solely on the contraindications section of the SPC.

The pictogram, added to most drugs since 2017, does not in itself provide all the information women need about drug treatment during pregnancy, but it sends out a strong and lasting general message that any drug thus labelled poses a risk in pregnancy. Healthcare professionals also need to remind patients that the absence of a pictogram does not mean that the drug is safe to use during pregnancy.

Patient leaflets and adverse effects: less information than in SPCs. The patient leaflets provided with drugs are supposed to give patients accurate information about their medication, to ensure that they use it correctly and avoid unnecessary harm. Leaflets must accurately reflect the information given to healthcare professionals in the latest version of the SPC. But we frequently find that patient leaflets omit information in the SPC about precautions, special warnings and adverse effects, thus putting patients at risk.

In late 2017, France's Orléans Court of Appeal confirmed that Sanofi Aventis was liable for malformations that occurred in a child exposed in utero to *valproic acid* (Dépakine°) (7). The pharmaceutical company argued that (our translations): "*the patient leaflet* [dated 19 July 2001], *drafted under the strict oversight of the Health Authority, also reflected the risk of teratogenicity, in compliance with the SPC*". This patient leaflet stated: "*inform your doctor if you are pregnant or hoping to become pregnant. Your treatment may need to be adjusted and specific monitoring will be necessary. At the time of the birth of your baby, careful monitoring of the newborn will be necessary*". But the Court of Appeal pointed out that the information in the SPC, which is intended for healthcare professionals and is not provided in the drug packaging, is no substitute for the information provided for patients in the package leaflet, and concluded that the 2001 patient leaflet for Dépakine° did not "*offer the safety that could legitimately be expected because it did not include teratogenicity among the possible adverse effects* (…) *which, when it occurs, is extremely serious* (…)" (7).

The patient leaflet for Delprim° (*trimethoprim*), which *Prescrire* examined in 2017, simply states that the drug should be avoided during the first trimester of pregnancy, and that patients who become pregnant during treatment should consult a doctor (8). The corresponding SPC mentions the risk of teratogenicity and provides details of the serious harms associated with *trimethoprim* use before and in early pregnancy.

Similarly, Gilead Sciences explains the absence of any mention of adverse effects in the patient leaflet for Epclusa° (*sofosbuvir* + *velpatasvir*) by an overly formalistic interpretation of the regulations (9,10).

In summary, report dangerous packaging. In 2017, many pharmaceutical companies continued to market both new and older drugs in dangerous packaging, accepted by health authorities that continue to set the bar for packaging quality too low. A drug's packaging must make it as safe to use as possible: by ensuring that the doses administered correspond to the doses prescribed, and by informing patients of the drug's adverse effects and interactions. Healthcare professionals have an important role to play by choosing drugs with the highest-quality packaging among the options available, by explaining any complex preparation or administration procedures to patients, and by reporting any packaging-related dangers they identify to drug regulatory agencies (see p. 195).

Review produced collectively by the Editorial Staff: no conflicts of interest

▶ Translated from *Rev Prescrire* **April 2018**
Volume 38 N° 414 • Pages 294-299

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Drug packaging in Europe: what factors drive progress?

A number of measures and guidelines have been introduced in Europe and France to improve the safety of drug packaging.

Progress arising from European guidelines. The implementation of a new European pharmaceutical directive in late 2005 improved the regulatory framework and guidelines in the EU, making medicines safer (1,2). Their impact on drug packaging was an improvement in the quality of the labelling of many new drugs, which prominently display the international nonproprietary names (INNs) of the active ingredients, and an improvement of patient leaflets through the introduction of readability testing.

In 2007, the European Medicines Agency (EMA) announced that it had strengthened its procedure for checking the labelling on packaging items before drugs are introduced to the market (3). The publication of a Council of Europe report in 2006 also provided a strong incentive for the EMA to recognise the importance of medication errors and their prevention (4). The EMA published a guideline on this topic in 2015, following a public consultation launched in 2013 (5).

In practice, drug regulatory agencies set the bar too low. Judging by the marketing authorisations which the EMA grants for oral drugs supplied in bulk bottles or with patient leaflets that lack important safety information, this agency does not take these positive developments sufficiently into account (6).

The same can be said for the French Health Products Agency (ANSM). Many drugs are authorised despite dangerous packaging flaws: labelling that trivialises important information for the prevention of medication errors, such as the INN, poor-quality dosing devices, and patient leaflets that lack important information present in the documentation intended for health professionals or with limited information about excipients. What's more, umbrella brands include drugs bearing the same easy-to-remember brand name but containing different active ingredients (7-10).

The ANSM has made some progress since 2015, issuing some much-needed recommendations that will greatly increase patient safety if put into practice: withdrawing umbrella brands, giving due prominence to INNs, and encouraging the use of unit-dose blisters and accurate dosing devices (6-9).

Progress driven by civil society. The progress made in Europe in the 2000s owes much to the work of the Medicines in Europe Forum, composed of organisations representing patients, consumers, mutual health insurance providers, and health professionals, including *Prescrire* (1). This progress is also due to the regular participation of various organisations in public consultations on drug packaging organised by drug regulatory agencies. The International Medication Safety Network (IMSN) and *Prescrire* contributed in this way to the ANSM recommendations in favour of the prohibition of umbrella brands in France in 2018 (1,6-16).

Campaigning of a French support group (Apesac) for the parents of children with birth defects caused by *valproic acid* played a major role in the introduction of a warning pictogram on boxes of drugs known to be dangerous during pregnancy in France in 2017 (17).

The patient leaflet for the HIV testing device Autotest VIH° shows the exceptional quality that can be achieved when patient organisations are involved, while the packaging of a similar device (Insti°), designed without the collaboration of patients, has many shortcomings (18,19).

Remain proactive. Healthcare professionals and patients also have a very important role to play by reporting packaging flaws that caused or could potentially cause medication errors. In 2017, several French hospital-based healthcare professionals reported the potential for error associated with the coexistence of dosing devices marked with different graduation scales for Haldol° oral solution (*haloperidol*).

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