Annual review of drug packaging: progress is too slow

- Prescrire examined the packaging of 190 medicinal products in 2022. Yet again, a few welcome advances were identified, but so were numerous flaws.
- A number of products were properly labelled and their safety improved by giving due prominence to the international nonproprietary name (INN), and by ensuring that different dose strengths are readily distinguishable.
- A few improvements in terms of convenience were noted, such as ready-to-use forms of injectable drugs, or solid oral forms packaged in precut unit-dose blister packs. However, too many drugs are still marketed in multidose bulk bottles.
- Some packaging known for its potential to cause errors was partially rectified, while other flaws persisted.
- The market introduction of a generic version of an existing product provides an opportunity to make the drug available in packaging that is safer and more convenient to use. These opportunities were too rarely seized in 2022, however.

A drug's packaging contains a set of components for use by patients, their caregivers and healthcare professionals. It is important that packaging is well designed with a view to ease of use and the prevention of errors with dangerous consequences. In 2022, Prescrire examined the packaging of 190 medicinal products featured in our French edition. What commendable packaging features did we find during these analyses? What flaws were observed? Did any of the packaging changes Prescrire identified in 2022 make the drug easier and safer to use?

International nonproprietary name and dose strength: key components of drug labelling

A drug's true name is the international nonproprietary name (INN) of the active substance it contains. The INN usually incorporates a stem, from which the drug's pharmacological action and adverse effect profile can be inferred to some extent. To be properly labelled, for identification purposes and to reduce the risk of certain dispensing and administration errors, a pharmaceutical product's primary packaging (the container in direct contact with the drug itself, such as a bottle, vial, ampoule or blister) and box must display the INN, followed by the dose strength, and sometimes its pharmaceutical form.

Preventing errors due to confusion between certain INNs. Using the INN when prescribing, as well as when thinking and communicating about drugs, is good professional practice and contributes to patient safety. One risk of marketing medicines under invented names that do not include the INN is that patients can unwittingly take the same active substance several times when it is contained in different brand-name products. There is also a risk of confusion between products, for example medicines with different compositions marketed under the same umbrella brand name.

But confusion can also arise between INNs, sometimes with serious consequences. One measure recommended by several drug regulatory agencies is to highlight the differences between look-alike INNs by using "tall man" or mixed case lettering on packaging (1-4). One example is *dobutamine*, which can be mistaken for *dopamine*. Tall man lettering has been used on the packaging of Dobutamine Sun° 5 mg/ml solution for infusion in prefilled syringes (French marketing authorisation), to display the INN in the product's name as "DOBUTamine".

Trastuzumab is an antineoplastic monoclonal antibody used to treat certain breast cancers. It is marketed as the standalone (unconjugated) antibody or conjugated to a cytotoxic agent in *trastuzumab emtansine* and *trastuzumab deruxtecan*. Particular care must be taken at every stage of the healthcare process to avoid confusion between products containing these different forms of *trastuzumab*. Fatal wrong-dose errors occurred during clinical trials through this mechanism (5). The INN *trastuzumab deruxtecan* is clearly displayed in bold face, and highlighted in orange, on the box and vials of Enhertu°, helping users to correctly identify the active substance present.

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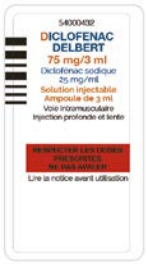
Enhertu° (*trastuzumab deruxtecan*)

INNs still too often absent or indistinct in 2022. As in previous years, the INN was hard to make out on the primary packaging of too many of the drugs we analysed in 2022, and in some cases, it was entirely absent. For example, the INNs are printed only once on the back of the blister pack of Xonvea° (*doxylamine + pyridoxine*) (French marketing authorisation), in very small characters. And the INNs are simply absent from the single-dose containers of Xiop° (*latanoprost*) and Zagrapa° (*ketotifen*) eye drops (French marketing authorisation).

Injectable forms labelled with the total quantity of drug present to prevent wrong-dose errors. The manner in which the dose strength of an injectable drug is expressed on its box and label can help prevent errors, by giving greater prominence to the total amount of active substance contained within the total volume present, rather than the quantity in each millilitre. For example, 75 mg/3 ml is displayed more prominently than 25 mg/ml on the packaging of Diclofenac Delbert° (*diclofenac*) solution for injection (French marketing authorisation). This makes users fully aware of the dose present in each container, be it an infusion bag, bottle, vial or ampoule. It is nonetheless helpful for dose preparation to have the quantity of drug per millilitre displayed, but in less prominent lettering (1,6).



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Diclofenac Delbert° (*diclofenac*)

Other examples of high-quality packaging on which the quantity of drug in the total volume present was clearly distinguishable from and more prominent than the concentration are the injectable drugs Armisarte° (*pemetrexed*), Dobutamine Sun°, Midazolam Viatris° (French marketing authorisation) and Oyavas° (*bevacizumab*).

This is not the case, however, for the various dose strengths of Midazolam Accord° (French marketing authorisation), where greater prominence is given on the ampoule label and the front of the box to the quantity of drug per millilitre of solution, even for the 5-ml and 10-ml vials.

Improvements in safety and ease of use in 2022?

High-quality packaging is intended to make drugs convenient and safe to use. There were a few noteworthy improvements in the drug packaging Prescrire analysed in 2022, but some changes represented a step backwards.

Ready-to-use injectable drugs. Ready-to-use forms of injectable drugs eliminate a preparation step and should be preferred, when available, because they act as a safeguard against wrong-dose errors. Irinotecan Sun° (French marketing authorisation) is the first injectable *irinotecan*-containing product to be marketed in France in pre-diluted form in a ready-to-use infusion bag. The other *irinotecan*-containing products available are marketed as a concentrate in vials, requiring a specialised team for dose preparation, including a dilution step at which errors can occur.

Dobutamine Sun° is another example of a welcome ready-to-use solution for injection, in this case for use in a syringe pump. It is the first ready-to-use *dobutamine*-containing product to have been marketed in France, saving healthcare professionals precious time in an emergency.

In December 2022, the French Health Products Agency (ANSM) published recommendations on its website aimed at reducing the incidence of sometimes fatal, wrong-dose errors involving concentrated *potassium chloride* solutions that must be diluted before administration. Prediluted solutions would help reduce errors and the life-threatening dangers associated with the use of concentrates, but unfortunately they are no longer marketed in France since mid-2020 (7,8).

Multiple injections required to achieve the recommended dose in the absence of appropriate dose strengths. Some of the drugs Prescrire examined in 2022 had been marketed at dose strengths that required 2 to 4 consecutive injections to achieve the recommended dose (9). This is the case with Adtralza° (*tralokinumab*) 150 mg solution for injection in pre-filled syringes. Each box of 4 syringes of Adtralza° contains 2 cartons, each containing 2 pre-filled syringes. A pictogram on the carton lid containing the word "*repeat*" is captioned "*Then, use both syringes. For a 300 mg dose, two 150 mg syringes are required. Inject one syringe after the other*". The contents of 4 syringes must be injected to achieve the initial 600-mg dose of *tralokinumab*.

Tysabri° (*natalizumab*) is supplied in a box, containing 2 pre-filled syringes, labelled "*Use two 150 mg syringes*" and "*Full dose=300 mg*", with a diagram showing 2 syringes on either side of a plus sign (+). The boxes of Bimzelx° (*bimekizumab*) pre-filled syringes and pens are similarly labelled.

Perhaps these printed warnings about the need for multiple injections to achieve the full dose will reduce the incidence of errors, but a more practical option for patients would have been to market these drugs in dose strengths corresponding to the recommended doses, including those cases where new indications were authorised for an existing product.

Dry oral forms: a few high-quality blister packs, but bulk bottles still on the market. High-quality blister packaging had been used for several dry oral forms (tablets or capsules) marketed in 2022. For example, Calquence° (*acalabrutinib*) comes in unit-dose blister packs, i.e. the back of each blister pocket is labelled with the INN, dose strength, expiry date

Packaging and covid-19: leniency no longer justified!

In 2020, the unfolding public health crisis necessitated an urgent response and a need to rapidly produce and market covid-19 vaccines and treatments. This haste led to flawed packaging design, and in turn errors.

Covid-19 vaccines: rudimentary labelling. In late September 2020, the European Commission decided to temporarily relax the regulatory requirements for the packaging of future covid-19 vaccines. These exemptions applied in particular to the labelling of boxes and vials, and the patient leaflet (1). Although the labelling of covid-19 vaccines has improved since their market launch, the "flexibilities" presented as temporary by the European Medicines Agency still appear to be in effect. For example, on the label on the vials of the vaccine Spikevax Original/Omicron BA.1®, neither INN is shown, there is no mention of "bivalent" or "BA.1", and the volume per dose is not specified. To distinguish this bivalent vaccine from the monovalent vaccine, it is labelled "0/O", which stands for "zero/omicron", which is not very informative and could lead to confusion between the two vaccines (2).

Paxlovid®: caution in renally impaired patients. The packaging of Paxlovid® (*nirmatrelvir* + *ritonavir*), a combination of an antiviral drug and an enzyme inhibitor, authorised for early treatment of covid-19, is also flawed. The box and blister packs are labelled with the code PF-07321332 where the INN *nirmatrelvir* should be. The blister packs are divided into 2 halves, each containing 2 tablets of *nirmatrelvir* 150 mg and 1 tablet of *ritonavir* 100 mg: one half of the pack is yellow with a sun symbol and is to be taken in the morning, and the other half is blue with a moon symbol to indicate that it should be taken in the evening. This packaging can lead to wrong-dose errors in patients with moderate renal impairment, for whom the recommended dose is 1 tablet of each substance per administration, rather than 2 tablets of *nirmatrelvir* + 1 tablet of *ritonavir*.

When Paxlovid® was first marketed in the United States, pharmacists were initially asked to remove the superfluous tablets from blister packs they dispensed for patients with moderate renal impairment. In some cases, pharmacists forgot to remove all of the superfluous *nirmatrelvir* tablets, or mistakenly removed the *ritonavir* tablet instead of one of the 2 *nirmatrelvir* tablets (3). Pfizer introduced a pack size suitable for patients with moderate renal impairment in the US in mid-2022, with 1 tablet of *ritonavir* 100 mg and 1 tablet of *nirmatrelvir* 150 mg in each half of the blister packs. The US patient leaflet for Paxlovid® was also revised in August 2022 to enable patients to make sure they received the pack size appropriate for their renal function. The labelling on the blister packs also provides clearer information about the dosage (3,4). The modified format, to reduce the risk of patients with moderate renal impairment receiving the wrong dose, is not available in France as of mid-2023.

It is time standards were restored. More than three years have elapsed since the pandemic began. There is no valid reason why the relaxed regulatory requirements should still apply to the packaging of covid-19 vaccines and drugs available in Europe.

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3- ISMP "Numerous wrong dose errors with Paxlovid". In: "ISMP Medication *Safety Alert*! Acute Care" 30 June 2022; **27** (13): 1-3.
4- ISMP "Pfizer and FDA respond to Paxlovid error reports". In: "ISMP Medication *Safety Alert!* Acute Care" 11 August 2022; **27** (16): pages 1-2.

and batch number. In addition, a sun or moon symbol on each blister pocket helps patients keep track of the time of day they need to take their medication.

The fixed-dose combination Biktarvy® (*bictegravir* + *emtricitabine* + *tenofovir alafenamide*) is supplied in a box of 30 tablets containing 5 non-unit-dose blister packs, and it is unfortunately also still marketed in bulk bottles. Four of these blister packs contain a week's supply of tablets, labelled with the days of the week, while the fifth, which has only 2 blister pockets, has a space on which to write the days of the week on which they should be taken. This packaging represents an advance, given the risks associated with bulk bottles, in particular the risk of spillage when handling the bottle and subsequent ingestion by a child.

Despite the advances noted in 2022, some drugs that are highly toxic when swallowed are still marketed in bulk bottles, such as the cytotoxic drug *hydroxycarbamide* (Siklos®), and the packaging of certain drugs was changed for the worse, such as the switch from blister packs to bulk bottles for Kaletra® tablets, containing a combination of the antiretrovirals *lopinavir* and *ritonavir*.

More should be made of opportunities to improve drug packaging

Improvements to drug packaging are rare and too slow. Sometimes, if errors occurred during clinical trials, the drug's packaging is modified before it reaches the market (10). More often, drug regulatory agencies ask pharmaceutical companies to improve a drug's packaging in response to errors or flaws reported after its market introduction. The arrival of generic versions is another opportunity to improve the quality and safety of health care, by making them available in better-quality packaging than was used for the originators. This opportunity is too rarely seized, however.

Partial improvements for multidose oral liquid drugs. The packaging of a multidose oral liquid drug should enable accurate dose measurement, for example by providing an easy-to-use oral syringe. It should also be equipped with a child-proof cap to reduce the risk of a child drinking the contents.

The oral syringe supplied with Zinnat° (*cefuroxime*) (French marketing authorisation) to measure paediatric doses used to have graduations corresponding to kilograms of body weight, but it is now graduated in millilitres. An oral syringe graduated in milligrams would have been a better choice, because the recommended doses are expressed in milligrams of the active substance in the summary of product characteristics (SmPC). The INN is still hard to make out on the box and the bottle label, and the oral syringe is not labelled with the drug's name.

The packaging of Bactrim° (*sulfamethoxazole + trimethoprim*, French marketing authorisation) oral solution is now more accurately labelled, and indicates the concentration of each substance in mg/ml. But other flaws persist, such as the presence of a dose-measuring spoon (less accurate than an oral syringe) and the absence of a child-proof cap on the bottle.

The labelling on the boxes and bottle labels of Contramal° and Topalgic° *tramadol* oral drops (French marketing authorisation) has been updated to specify that the solution must only be administered with the dropper, and to add the quantity of *tramadol* per drop, but these measures are not sufficient to prevent overdose. It is regrettable that highly concentrated *tramadol* solutions in inaccurate dropper containers remain on the market. A bottle containing a weaker solution, supplied with an oral syringe graduated in milligrams, would have been a better choice and a welcome improvement to reduce the risk of overdose.

Packaging of a generic: why not improve on the originator? The INN *tacrolimus* is not given due prominence on the box or blister packs of Conferoport° (*tacrolimus*, French marketing authorisation) prolonged-release hard capsules, a generic version of Advagraf°. Treatment with prolonged-release *tacrolimus* often requires several capsules to be taken at the same time, once daily, and although this is stated on the box of Advagraf°, it is not mentioned on the boxes of Conferoport°. The omission of this information could lead to wrong-dose errors.

An invented name was also chosen for Closalis° (*dexamethasone + calcipotriol*) gel (French marketing authorisation), a generic version of Daivobet° (*betamethasone + calcipotriol*). The INNs are barely discernible on the box and the tube of gel. And while the box for Daivobet° warns of the dangers of using this drug during pregnancy, by means of a pictogram adopted for this purpose in France, the packaging of Closalis° has no such warning. Why would two such similar products not provide the same level of warning to patients who are or could become pregnant?

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Daivobet° (*dexaméthasone + calcipotriol*)

In summary: progress has been too limited given the importance of this issue

Prescrire's editorial staff were pleased to see a few positive developments in safety or convenience of use in the packaging they examined in 2022, especially through labelling that rendered the drug and its dose strength clearly identifiable. There were, however, a few regrettable cases where changes represented a step backwards and, above all, many missed opportunities to improve various aspects of a product's packaging. To achieve safe, effective, user-friendly packaging, it must be considered as a whole. Drug packaging does not appear to be a major concern for pharmaceutical companies, which often make only minimal adjustments when actual changes must be made. Yet it is their responsibility to market new pharmaceutical products, including generics, in high-quality packaging, and also to rectify identified flaws. And it is up to drug regulatory agencies to make sure that companies do this job well, demand higher standards in general, and refuse to settle for superficial tweaks while dangers persist.

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

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