Annual review of drug packaging: choose high-quality packaging for safer health care

- Prescrire examined the packaging of 190 medicinal products in 2021. The results were mixed, with a few signs of progress alongside persistent or recurrent flaws.
- A marked difference was seen between products authorised through the European centralised procedure and those authorised through the French national procedure, with the international nonproprietary name (INN) all too often printed indistinctly on the boxes of the latter, overshadowed by the more prominent brand name.
- The box of some medicinal products is printed with useful information for patients on how to take the drug properly, helping to inform patients about their treatment from the moment it is dispensed.
- In a few exceptional cases, tablets or capsules previously marketed in bulk bottles were upgraded to unit-dose blister packaging. Precut unit-dose blister packaging was unfortunately rare among recently authorised products.
- Some new oral liquid drugs marketed in multidose bottles came with a graduated oral syringe, a device well-suited to measuring doses of such drugs. But many older oral liquid drugs are still supplied with inaccurate dosage delivery devices.
- The marketing of injectable drugs in a ready-to-use form is helpful to both patients and healthcare professionals.
- If health care is to be provided safely, it is essential that drugs be available in high-quality packaging as soon as they come onto the market. It is imperative that pharmaceutical companies and regulatory agencies pay particular attention to drug packaging when compiling, or evaluating, applications for marketing authorisation.

A drug's packaging makes an important contribution to the quality of health care and to the safety of patients and the people around them.

Prescrire examined the packaging quality of 190 medicinal products in 2021. Some progress was observed, including improvements to products that were already on the market, while a number of new products entered the market in poor-quality or even dangerous packaging. Yet the packaging of some products that have been on the market for years is still in need of improvement to reduce the risk it poses to patients.

There were even occasions when pharmaceutical companies and agencies made decisions that reduced the quality of a drug's packaging, and therefore patient safety.

Information on the box to help identify and use the drug correctly

A drug's primary (or immediate) packaging is the layer in direct contact with the drug that protects it from the external environment, such as a blister pack containing tablets, a bottle containing an oral solution, or an ampoule containing an injectable solution. The next layer is the box (or secondary or outer packaging). Both of these layers provide useful surfaces on which to display information to help correctly identify and use the drug.

INNs not always clearly displayed on the box. The first step in identifying a drug is usually through its box, based on its size, colour scheme, graphics and the specific information printed on it, especially the drug's name or names. Each medicinal substance a product contains must be clearly identified by its true name, i.e. its international nonproprietary name (INN).

INNs tend to be clearly displayed on the boxes of medicinal products granted marketing authorisation through the European centralised procedure.

INNs were hard to make out and overshadowed by the brand name on the boxes of some other products Prescrire examined in 2021. Many of these products entered the French market after being authorised through the national procedure by the French Health Products Agency (ANSM).

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A general drawback of brand names for fixed-dose combinations is that users can easily forget that the product contains more than one drug (1).

In the case of inhaled drugs, errors can result from giving prominence to the brand name of the inhaler device as well as that of the medicinal product, leading to confusion between products supplied with the same inhaler but containing different drugs (2).

Information on the box on using the drug correctly. The box is a useful surface on which to print information that helps ensure the proper use of drugs. When a drug is taken or administered in an unusual way, it is useful to indicate this on the box, in order to bring it to the attention of healthcare professionals and patients when they dispense, administer or take the drug.

For example, the box of Xeljanz° (*tofacitinib*) 11 mg prolonged-release tablets bears the warning, printed in bold, "Do not crush, split or chew". No such warning is present on the box of Sinemet° 200 mg *levodopa* + 50 mg *carbidopa* prolonged-release tablets, which in addition are scored, wrongly suggesting that they can be split in two; yet this would alter of rate of absorption of the drug substances they contain (3,4).

In order to prevent errors that the pharmaceutical company attributed to community pharmacies dispensing *risedronic acid* film-coated tablets (taken on an empty stomach before breakfast) instead of Actonel° 35 mg gastro-resistant tablets (taken after breakfast), its packaging was updated in 2021. However, there is no reminder on the new boxes of Actonel° 35 mg gastro-resistant tablets to take these tablets after breakfast, even though they are less effective when taken on an empty stomach (5). And one aspect of the new packaging represented a step backwards, in that the reminder to take "*one tablet per week*" became less visible. Patients may therefore benefit from being reminded of this dosing frequency by the dispensing pharmacist.

Primary packaging: protective in several ways

The primary packaging is the layer in direct contact with the drug. It offers an additional surface on which to display the information required to identify the drug and use it correctly, and it is crucial if the drug is to remain readily identifiable when removed from its box. The primary packaging also helps protect people in contact with the patient, especially if it deters vulnerable people, such as children, from ingesting the drug.

Bulk bottles: still too common. Too many drugs in dry oral form were still marketed in bulk bottles in 2021. Once removed from the bottle, for example to place them in a weekly pill organiser, these tablets or capsules are often impossible to identify. Bulk bottles pose other dangers, such as accidental poisoning of a child if the contents of the bottles are spilled, or exposure of the patient's family to cytotoxic drugs, such as Ayvakyt° (*avapritinib*) tablets and Vitrakvi° (*larotrectinib*) capsules (3,6).

Unit-dose blisters, the best choice. Pre-cut unit-dose blisters are the first-choice primary packaging for dry oral dosage forms, such as tablets or capsules (7). The back of each blister pocket must be labelled with the drug's INN and the product's brand name, dose strength, batch number and expiry date, to ensure that the product it contains can be correctly identified when the pocket is detached from the rest of the pack. Too few of the medicinal products we examined in 2021 were packaged in pre-cut unit-dose blisters.

The market introduction of a generic version of an existing drug provides an opportunity to use better-quality packaging than that used for the originator. This was the case for Deferiprone Arrow° tablets, which were marketed in unit-dose blisters, while the originator, Ferriprox°, is still marketed in bulk bottles.

Similarly, the generic Hydrochlorothiazide Arrow° is available in hospitals in 12.5-mg tablets packaged in pre-cut unit-dose blisters. However, patients in the community only have access to 25-mg strength tablets, and the identifying information is dotted around the blister pack at random rather than being fully printed on each blister pocket.

Pharmaceutical companies sometimes chose to improve the packaging of a drug that is already on the market. This was the case for Imbruvica° (*ibrutinib*), previously marketed in capsule form in bulk bottles, but now marketed in tablet form in blister packs.

Poorly designed blister packs. Blister packs are not always designed to ensure that the drug is readily identifiable and to minimise the risk of errors. If the important information is dotted around the blister pack at random, detached blister pockets are no longer fully labelled.

Poorly designed pre-cut lines can also cause errors. For example, the pre-cut lines in the blister strips of Nubeqa° (*darolutamide*) divide them into sections that contain 4 tablets each. Each tablet contains 300 mg of *darolutamide*, but "Nubeqa° 300 mg" is only printed once on each section. Confusion over whether all 4 tablets or just one tablet provides a dose of 300 mg could result in overdoses (3).

Ease of use and safety

A drug's packaging must be designed to ensure that it is convenient and easy to use, without posing a danger to the patient and those around them.

A long overdue but welcome upgrade to reduce the risk of confusion. Wrong-route errors, involving intramuscular or subcutaneous injection, have occurred with the *rotavirus vaccine* Rotarix° oral suspension due to the resemblance of its oral applicator to a syringe. In 2021, after 15 years on the

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market, the syringe was finally replaced with a squeezable tube containing the oral suspension (8).

Oral syringes graduated in milligrams eliminate the need to convert milligrams into millilitres. Most of the recently authorised oral liquid drugs in bottles that Prescrire examined in 2021 were supplied with an oral syringe with which doses could be accurately measured. None of these syringes was graduated in milligrams, however. Yet, for liquids at concentrations other than 1 mg/ml, a syringe graduated in milligrams is preferable, because it eliminates the need to perform a calculation to convert milligrams into millilitres.

The oral syringes supplied with Fintepla° (*fenfluramine*) and Fycompa° (*perampanel*) are graduated in millilitres, and the one supplied with Tiorfan° (*racecadotril*) is graduated in kilograms of the child's body weight, which makes it difficult to keep track of the quantity of drug administered.

We observed some progress on this front. Loxapac° (*loxapine*, French marketing authorisation), for example, used to come with an oral syringe graduated in millilitres, but it has now been replaced with a syringe graduated in milligrams. However, in some cases, the change in delivery device represents a step backwards: the syringe supplied with Rovalcyte° (*valganciclovir*), for example, is now graduated in millilitres (3).

Inaccurate or absent dosing devices. Some generics are marketed with the same packaging flaws as the originator. For example, like the originator, Aripiprazole Arrow° is supplied with two dosing devices: a dropper and a measuring cup, both of which are inaccurate devices and graduated in millilitres. No dosing device has been provided with Vitrakvi° (*larotrectinib*) oral solution, which is particularly unacceptable considering that it is an antineoplastic drug and that protective measures are therefore necessary when handling it (3).

Our analyses show excessively slow progress in improving the dosing devices provided with many oral liquid drugs that have been authorised in France for many years. In 2021, the *pholcodine* syrups Biocalyptol°, Biocalyptol Sans Sucre° and Pholcodine Biogaran° usually come with a measuring cup graduated in millilitres, an inaccurate type of dosing device. Dimétane Sans Sucre° (*pholcodine*) comes with a double-ended measuring spoon, with a 2.5-ml capacity bowl at one end and a 5-ml capacity bowl at the other end, which can also cause errors.

Dropper bottles: too inaccurate. In 2021, too many drugs were still supplied in dropper bottles, sometimes containing highly concentrated solutions that can be particularly dangerous in the event of a manual error or overdose, such as *tramadol* or certain neuroleptics (9,10). Although dropper bottles can sometimes be used to administer low doses, which is useful in practice when a treatment must be introduced or withdrawn gradually, they are inaccurate and can cause errors through manual errors or by miscounting the number of drops, especially when preparing a high dose.

The packaging of Laroxyl° (*amitriptyline*) oral solution (French marketing authorisation) underwent a chaotic update, illustrating how a company's effort to improve patient safety can end in failure. The dropper bottle was replaced in 2021 by a bottle with a dosing syringe graduated in milligrams, which the company explained was to (our translation) "*improve correct use and reduce the risk of medication errors*". It was an improvement. However, the first graduation on the syringe was 10 mg, and although this corresponds to the lowest dose mentioned in the summary of product characteristics (SPC), it cannot be used to measure lower doses, which are sometimes useful in clinical practice. As a result of this flaw, the company brought the dropper bottle back onto the market, despite the risk of dosing errors through miscounting the number of drops. However, the number of milligrams of drug per drop is now displayed more clearly on the box (11).

Injectable products: ready-to-use forms are safer

The advantage of ready-to-use forms, such as pre-filled syringes or pens, or injector pens with a dose selector, is that they reduce the risk of errors specific to injectable products and are easier to use.

Well-designed syringes and pens. Some of the injectable medicinal products we examined in 2021 came in a ready-to-use form, such as Entyvio° (*vedolizumab*) and Remsima° (*infliximab*), authorised in pre-filled syringes and pens for subcutaneous injection.

Generic versions of *pegfilgrastim* (Cegfila° and Nyvepria°) and *tildrakizumab* (Ilumetri°) have also been recently authorised in pre-filled syringes. The boxes and labels of these products clearly show the INN and dose strengths, and they are equipped with a system to cover the needle after use, to prevent accidental injuries.

The cartridge form of Apokinon° (*apomorphine*, French marketing authorisation) was an advance. The cartridges are inserted into the Crono PAR° pump, eliminating the need to fill the reservoir using a syringe and a needle (12).

The usefulness of some ready-to-use injectable products, however, was marred by flaws.

Lack of a needle guard. There is no system on Takhzyro° (*lanadelumab*) pre-filled syringes to cover the needle after use, to prevent accidental injuries (13).

A misleading trademark. The Lyumjev° range of pens, containing *insulin lispro* with treprostinil and sodium citrate as excipients, includes some pre-filled pens containing a solution at a concentration of 100 units per ml, oddly named Lyumjev° Junior Kwikpen, even though the drug has not been authorised for use in children. The packaging is labelled with the INN *insulin lispro* but not with the excipients,

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yet the company claims that this insulin has an earlier onset of action because of these excipients (14). Confusion is therefore possible with other products containing *insulin lispro* without these excipients, for example those of the Humalog° product line.

Risk of confusion between a new dose strength and the old one. New dose strengths of *enoxaparin* (Lovenox° 12 000 units and 15 000 units of anti-Xa activity, French marketing authorisation) have been marketed in pre-filled syringes containing a solution at a concentration of 15 000 units per ml, while the other dose strengths in the product line contain a solution with a concentration of 10 000 units per ml. The Lovenox° product line now includes syringes containing the same volume of solution (0.8 ml), but either 8000 units or 12 000 units of *enoxaparin*. It also includes syringes containing 1 ml of solution, some of which contain 10 000 units of *enoxaparin* and others 15 000 units. Errors with potentially serious consequences could occur if the dose were prescribed in millilitres. There are no warnings about the risks associated with this new concentration on the packaging of the new dose strengths of Lovenox°. The syringes are graduated in milligrams and millilitres, whereas doses are expressed in units of anti-Xa activity and milligrams in the SPC (15).

Take care with overfilled syringes. Eylea° (*aflibercept*) pre-filled syringes are overfilled, so that the air present in the needle can be expelled along with the excess volume. Before administering the drug by intravitreal injection, the plunger of the pre-filled syringe must be depressed until it aligns exactly with the "dosing line". Elevated intraocular pressure has been reported more frequently with the pre-filled syringes marketed in 2021 than with the injectable solution in vials, which had to be taken up into a syringe. These adverse effects were attributed to manual errors, especially failure to align the plunger with the dosing line when preparing the dose, then injecting the excess volume present in these pre-filled syringes (16).

Lack of a ready-to-use form. In some cases, doses are difficult to prepare and administer, or errors occur, because no ready-to-use form is available. These problems are amplified when the equipment required to inject the drug is not provided, especially for products available in the community, as is the case for Givlaari° (*givosiran*), Hemlibra° (*emicizumab*), Nulojix° (*belatacept*) and Oxlumo° (*lumasiran*). With *plerixafor* (Mozobil°), very small-volume injections are required for some children, which is wasteful and can cause dosing errors.

Various temporary exemptions from European law were granted for multidose bottles of vaccines used in covid-19 immunisation campaigns (17).

In summary: an urgent need to improve drug packaging

Our analyses of the packaging of the medicinal products featured in *Prescrire* in 2021 produced mixed results yet again, including both tangible improvements and major (and unfortunately recurrent) flaws.

Too often, it is only when errors are reported to regulatory agencies after a product's market introduction that its packaging is finally improved. Yet the design of a drug's packaging is an important part of drug development. It should be carefully thought through and evaluated well before the drug is marketed, taking into account how healthcare professionals work and the errors observed in clinical trials, and anticipating the difficulties patients are likely to encounter (18).

In the interests of patients, companies should be required to develop high-quality, safe packaging, and drug regulatory agencies should pay more attention to packaging quality when evaluating and authorising drugs.

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