2019 drug packaging review: slow progress and dangers

ABSTRACT

- ***Prescrire*** **examined the packaging quality of 173 medicinal products in 2019. Despite some improvement in recent years, albeit slow, there are still many drugs on the market with dangerous packaging. The pharmaceutical industry seems unaware of a range of long-known and easily avoidable packaging flaws.**

- **The French Health Products Agency (ANSM) is having a hard time getting pharmaceutical companies to follow its guidelines on the selection of proprietary names, labelling and safer dosing devices.**

- **Year after year, old products, only authorised at the French level, account for a large proportion of the flaws and dangers identified in our packaging analyses, with the self-medication sector being a particular offender. Marketing authorisation procedures involving the European Medicines Agency (EMA) led to some advances in drug packaging, but weaknesses persist, particularly with regard to the safety of children.**

- **Patients are benefiting from improvements to patient leaflets thanks to the European framework but, in 2020, health authorities urgently need to improve and harmonise the information provided on the risks drugs pose during pregnancy.**

- **Healthcare professionals are at the forefront in preventing packaging-related errors, and in identifying and reporting packaging flaws, in order to protect patients.**

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Almost 20% of the 173 pharmaceutical products examined by *Prescrire* in 2019 received a Red Card in our annual Packaging Awards because their packaging could be, or has proved to be, dangerous (see *Prescrire Int* n° 213 pp. 79-80). Overall, however, the situation has been improving for the past 20 or so years, albeit very slowly, due to the centralised European framework provided for the authorisation of medicinal products, which is clearly more conducive to safe packaging and prevention of medication errors (1,2).

In 2019, 70% of these Red Cards were given to products authorised in France at the national level alone, 70% of which were granted marketing authorisation before the year 2000. In other words, pharmaceutical companies have had at least 20 years to make these products safe to use since their authorisation, but have not done so.

Slow improvements despite known dangers

The quality of a drug's packaging is determined by many factors, starting with the design proposed during drug development, then for the marketing authorisation application. It also depends on the series of industrial processes culminating in each sales pack, containing the pharmaceutical form (e.g. tablets, oral solution) in its labelled primary and secondary packaging, together with other items, including the patient leaflet and a dosing device where necessary. In the European Union, pharmaceutical companies are required to provide a patient leaflet with medicinal products. Other aspects of drug packaging are subject to regulatory requirements,

such as the presence of the drug's international nonproprietary name (INN) and certain pictograms (2).

Too many quality standards are optional. However, many aspects of drug packaging that help increase medication safety are not regulated. For example, pharmaceutical companies are not required to: display the INN in larger characters than the drug's brand name; systematically package tablets in perforated unit-dose blisters in which each unit is labelled with the drug's name, dose strength, pharmaceutical form, batch number and expiry date; equip all bottles containing oral liquid drugs with a child-proof cap; develop a specific dosing device for each multidose oral liquid drug; and update a drug's packaging when its indications are extended to include patients requiring low doses, such as young children. To encourage manufacturers to do more than the bare minimum, health authorities in some EU member states have added layer upon layer of standards over the past decades, aimed at improving the safety of patient leaflets, labelling and dosing devices (2,3). Unfortunately for patients, these standards remain optional.

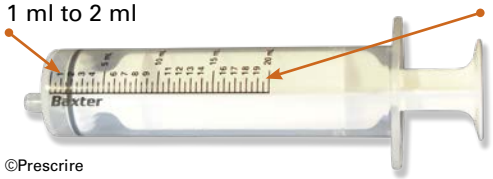
There are products on the market that show how many technical solutions are available for improving the quality and safety of packaging, but manufacturers have been slow to adopt them. And the many flaws and dangers that persist year after year show how drug packaging is often neglected, despite being an integral part of a medicinal product's harm-benefit balance.

Persistent dangers. The types of packaging flaws we identified as dangerous in 2019 have all long been known to health authorities:
– undue prominence given to the promotional components of the labelling (brand name, brand graphics, company logo), potentially obscuring the information that is essential for health care, such as INNs and dose strengths;
– dosing device absent or not specifically adapted for the drug;
– drugs that are not ready to use or are too complex to prepare for patients or carers;
– blister packs or bottles that allow children easy access to the drugs they contain; etc.

Drugs intended for self-medication, available without a prescription, were most likely to receive a Red Card in the *Prescrire* Packaging Awards (4). Most were authorised directly at the national level, by the French Health Products Agency (ANSM) (5).

20-ml oral syringe: delivers 10 times the paediatric dose

Dose to measure out for an infant: 1 ml to 2 ml



Graduations up to 20 ml lead to inaccuracy and errors. Inovelon° (*rufinamide*)

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ANSM's 2018 guidelines on labelling have had little impact

In 2018, the ANSM published guidelines to improve the safety of drug labelling and brand names which, in practice, applied mainly to self-medication products. If these guidelines were systematically applied, there would be no more umbrella brands, which combine multiple dangerous flaws, including:
– undue prominence is given on the box to the brand name (e.g. Actifed°, Advil°, Clarix°, Humex°, or Vicks°), shared by a range of drugs with very different compositions, indications and target populations;
– tiny, indistinct lettering is used for the INNs of the drugs they contain, including drugs that are more dangerous than useful according to *Prescrire*, such as *pseudoephedrine* (this flaw was identified on all the *pseudoephedrine*-containing products we examined in 2019);
– in contrast to ANSM guidelines, the most eye-catching features of the labelling are promotional, especially the brand name and company logo, and the same brand graphics used throughout the product line (6).

These guidelines had not yet had an impact on the packaging examined by *Prescrire* up to late 2019. A few exceptions aside, umbrella brands remain on sale in pharmacies, and patients remain exposed to their dangers. According to the ANSM, in response to our query, these guidelines have had a dissuasive effect on new umbrella brand applications, but little impact as yet on existing brands. One advance is worth mentioning, however: Galderma, which used to market a drug and some cosmetics under the brand name Curaspot°, has now changed the name of the cosmetics, thus distinguishing them from the drug. And in a welcome and rarely seen move, the company withdrew all the batches belonging to the umbrella brand Curaspot° from the market (7).

It is not only in umbrella brands that too little prominence is given to INNs. Examples include: Cozidime° (*dorzolamide* + *timolol*), Nicopatchlib° (*nicotine*); Phénergan° tablets (*promethazine*); and Praxilène° (*naftidrofuryl*).

Dose strengths are not always sufficiently clear. This is a serious flaw for drugs that soon build up to dangerous levels when taken in excess, such as *paracetamol*; yet the *paracetamol* content of Dolko° is hard to see on the box and even harder to see on the bottle. Previously, the *paracetamol* content of Fervex° (*paracetamol* + *pheniramine* + *vitamin C*) was not stated on the front of the box, but this was remedied in 2019. Paradoxically, the ANSM has the power to demand that pharmaceutical companies add the warning "*OVERDOSE = DANGER*" to boxes of *paracetamol,* but not to demand that the INN and dose strength be prominently displayed (8).

It is also dangerous to market different dose strengths in look-alike packaging. This is the case for Siklos° (*hydroxycarbamide*), available in 100-mg and 1000-mg strength tablets; yet confusing one for the other could lead to serious haematological adverse effects in children. The same type of flaw

exists with Fluimucil° expectorant (*acetylcysteine*) 200 mg and 600 mg.

It is perfectly possible to label drugs properly. The INNs and strengths of an increasing number of drugs marketed under an invented name are clearly displayed, and not overshadowed by promotional features. *Prescrire* has noticed in its packaging analyses that most of these products were licensed through a European procedure, usually the centralised procedure. For example, the INNs of the following products examined in 2019, licensed through a European marketing authorisation procedure, were clearly legible: Hemlibra° (*emicizumab*); Gilenya° (*fingolimod*); Tremfya° (*guselkumab*); and Pelmeg° (*pegfilgrastim*). The INN *mifepristone* is actually more prominent than the brand name Mifégyne°.

INNs are in effect clearly displayed when the brand name is a combination of the INN and the name of the company, rather than an invented name. This naming strategy is very common for generic drugs. For example, the INN is much more legible on the labelling and in the patient leaflet for Mylan's generic version of the *etonogestrel* + *ethinylestradiol* contraceptive ring than on the originator, Nuvaring°. Another advance provided by some generic manufacturers is to make a drug available in unit-dose blister packs when it was previously only marketed in bulk bottles (1).

More rarely, a generic can be less safe than the originator. For example, the blisters of Suboxone° (*buprenorphine* + *naloxone*) were protected by a child-proof film that some generics lack (9).

Bulk bottles: methotrexate tablets still marketed in bulk bottles, sometimes even without a child-proof cap

Methotrexate is a cytotoxic drug, also used at low weekly doses as an immunosuppressant in rheumatoid arthritis and some types of psoriasis. The danger is that patients may mistakenly take it daily rather than weekly, and fatal errors are in fact regularly reported. The bulk bottle for Novatrex° was finally replaced with blister packs in 2017, after 20 years on the market. The same is true for Imeth° 2.5 mg (since 2018), but not for Imeth° 10 mg or Méthotrexate Bellon°, both marketed in bottles without a child-proof cap (10).

The measures recommended by the European Pharmacovigilance Risk Assessment Committee (PRAC) to avoid dosing errors are welcome but limited. But the European Commission, responsible for ratifying these measures, has given the pharmaceutical industry until late 2023 to package all *methotrexate* tablets in unit-dose blisters (10).

In France, the ANSM has recommended perforated unit-dose blister packs as the quality standard for the labelling and safety of all tablets and capsules, whatever drug they contain. But they remained rare among the packaging examined by *Prescrire* in 2019:

Deroxat° (*paroxetine*): an inaccurate dosing device (measuring cup) + 2 scales (in mg and ml)

20 ml of a 2 mg/ml suspension contains 40 mg of *paroxetine*

20 mg of *paroxetine* risk of confusion with 20 ml

5 mg of *paroxetine* prescribed? Be sure not to measure out 5 ml, i.e. 10 mg!

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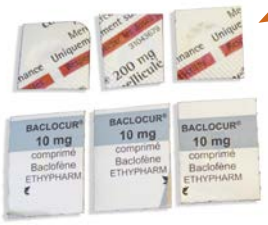
Blister packs without, and with, unit-dose labelling



Praxilène° 200 mg (*naftidrofuryl*) supplied in non-unit-dose blisters: separated doses are no longer identifiable

Baclocur° (*baclofen*) supplied in perforated unit-dose blisters with a child-proof film: each separated dose is identifiable

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for example Baclocur° (*baclofen*) (see illustration) and Flucortac° (*fludrocortisone*).

Pay attention to dosing devices to protect patients from errors

To reduce costs, most oral liquid drugs are supplied with a standard mass-produced dosing device graduated in millilitres, rather than a specific dosing device designed to suit the dosing recommendations for each clinical situation (drug, indication, and patient), determined through clinical evaluation.

Five of the 21 multidose oral liquid drugs examined in 2019 had no dosing device at all: ClarixToux Sèche Adulte° (*pentoxyverine*); Maxilase° and Alfa-Amylase Biogaran Conseil° (*alfa-amylase*); Potassium Liberty Pharma° (*potassium*); and Vicks Sirop Pectoral° (*pentoxyverine*). They were all authorised at least 20 years ago through the French procedure. The generic Alfa-Amylase Biogaran Conseil° was authorised about a decade after Maxilase°, without rectifying this omission.

Another type of flaw is choosing a graduated measuring cup as a dosing device. According to the US Food and Drug Administration (FDA), measuring cups are inaccurate in practice (11). Having examined hundreds of measuring cups, *Prescrire* has reached the same conclusion. Several products examined in 2019 were marketed with a measuring cup, such as the antidepressant Deroxat° (*paroxetine*) and the neuroleptic Phénergan° (*promethazine*). Worse yet, the measuring cup for *paroxetine* had two graduated scales, one in milligrams of the drug and the other in millilitres, a known source of confusion resulting in double or half doses because the drug is a 2 mg/ml suspension. Superfluous graduations also lead to confusion and errors. The measuring

cup, added to Potassium H2 Pharma° in late 2019, only displays the 2 volumes recommended (5 ml and 15 ml), which is an improvement over the measuring cups that systematically displayed 4 volumes: 2.5 ml, 5 ml, 10 ml and 15 ml. The 2.5-ml and 15-ml volumes indicated on the cup for Phénergan° syrup are unnecessary and could cause errors.

Very few dosing devices examined in 2019 had been improved, although a better syringe was supplied with Oxynorm° oral solution (*oxycodone*), graduated in milligrams rather than in millilitres.

In some cases, partial improvements led to inconsistencies. Thirty years after the market introduction of Nausicalm° syrup (*dimenhydrinate*), the box now contains an oral dosing syringe. But the patient leaflet still recommends the use of a household spoon for adults, and the dosing schedule on the box has not been updated and still refers to teaspoons. In another example, Vitamine K1 Cheplapharm° (*phytomenadione*) is now available in boxes of 1 rather than 5 ampoules, which was an excessive quantity given the recommended doses and had resulted in overdoses. But the measuring pipette still has a superfluous 1-mg graduation that could result in the administration of half the recommended dose of 2 mg. In a final example of partial improvement, after two patients died from dosing errors, Phosphoneuros° was marketed with a more precise syringe (1 graduation per 5 drops instead of 10). However, it cannot be used to prepare doses of fewer than 5 drops and is therefore unsuitable for neonates weighing less than 5 kg.

Risks during pregnancy: patient leaflets are ambiguous and not kept up to date

Marketing authorisations granted by the European Medicines Agency (EMA) provide an opportunity to make patient leaflets clearer and more informative, but they are not updated in a timely fashion. A notable example in 2019 is the patient leaflet for Ellaone° (*ulipristal*), which does not mention that the efficacy of this emergency contraception is reduced if hormonal contraception is used within 5 days of taking *ulipristal*.

For some years now, we have found the information about the risks associated with taking nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy to be ambiguous. The risks to the unborn child include malformations with first-trimester exposure, and renal harms or pulmonary hypertension with exposure from the 4th month onwards (12). The "*Do not take* (…)" section of 3 of the 9 patient leaflets for NSAIDs we examined in 2019 informed patients to never take NSAIDs at any stage of pregnancy. But in some cases, other sections of the same patient leaflet undermined this message with statements such as "*unless your doctor tells you to*" (Rhinureflex°, Nurofen Rhume°). In 6 other patient leaflets, the NSAID was only contraindicated from the 6th or 7th month of pregnancy onwards, but recommended one of four different strategies to women before this period:
– avoid the drug before the end of the 6th month of pregnancy, unless advised otherwise by your doctor (Ipraféine°);
– ask your doctor or pharmacist for advice in the first 6 months of pregnancy (Flurbiprofène Sandoz Conseil°);
– if *ibuprofen* is taken before the end of the 5th month of pregnancy, it must be used at the lowest possible dose for the shortest possible duration (Rhinadvil Rhume°);
– if necessary, and advised by your doctor, occasional use before the end of the 5th month of pregnancy (Entalgine°, Strefen°, Strefen Orange Sans Sucre°). The patient leaflets for these three products are actually the only ones that explain some of the risks "*in particular cardiopulmonary and renal risks, even after a single dose*".

In 2020, the parts of patient leaflets that deal with risks during pregnancy are still among the hardest to interpret.

Children: drug companies and agencies too often overlook their safety

Children once again remained the most overlooked patient group in 2019, in terms of the risks associated with unsuitable drug packaging. Half of the Red Cards in the 2019 *Prescrire* Packaging Awards were given to products whose packaging poses a danger to children, in particular due to the risk of error during dose preparation and the risk of accidental ingestion.

Multidose bottles still marketed without a child-proof cap. The Red Cards given for marketing an oral liquid drug (*alfa-amylase*, *dimenhydrinate*, *paracetamol*, *pentoxyverine*, *phosphorus*, *potassium*, or *promethazine*) in a multidose bottle without a child-proof cap were for products only licensed by the French regulatory agency between 1984 and 2001. The manufacturers of these products are under no obligation to add a child-proof cap, and have let this dangerous situation continue for 20 to 30 years.

Paracetamol: a profusion of products but none optimally packaged for paediatric use. In 2019, we examined the packaging of oral liquid preparations containing *paracetamol* available from pharmacies in France, in particular for children of all age groups. All the multidose oral liquid forms were supplied with a syringe graduated in kilograms of the child's body weight, calibrated to deliver 15 mg per kg, when 10 mg might suffice; one bottle lacked a child-proof cap (Dolko°); no ready-to-use sachet form was available to accurately administer a dose to an infant weighing less than 5 kg without having to measure it; and all of these products contained at least one excipient with known harmful effects. In practice, none of these products was completely suitable for purely paediatric use, despite the frequent use of *paracetamol* in children.

Extensions of indications to include paediatric use: EMA not fulfilling its role. Drugs are often first authorised for use in adults. When their marketing authorisation is later extended to include paediatric use, their packaging is not always adapted accordingly, or is insufficiently adapted. This is a failing of marketing authorisation extension procedures, including European centralised procedures, under the responsibility of the EMA. To name but two examples: the capacity of the oral syringe for Inovelon° (*rufinamide*) was left unchanged, yet it is far too high for infants; and the injection syringe for Firazyr° (*icatibant*) also remained unchanged, yet graduations corresponding to the doses appropriate for young children should have been added.

Failure to include the equipment needed to prepare paediatric doses is nothing new. We observed it in 2018 with Renvela° (*sevelamer*) and Vimpat° (*lacosamide*), and in 2017 with Kuvan° (*sapropterin*) (1,2).

It is unacceptable that, in France, the packaging for the oral vaccine Rotarix° (*rotavirus vaccine*) still contains a delivery device resembling a syringe for subcutaneous or intramuscular injection, which has resulted in accidental injection of the vaccine. It is especially unacceptable since the European SPC for this vaccine mentions another device that does not look like a syringe, which would eliminate the risk of mistaken injection.

A Packaging Award for clear, informative instructions for use provided with a paediatric drug

Examples of high-quality paediatric packaging and information do however exist.

The 2019 Packaging Award was attributed to Isentress° granules for oral suspension (*raltegravir*) for the quality of its "instructions for use" booklet. Since 2017, we have seen several paediatric drugs authorised by the EMA in powder or granule form. The child's carer must reconstitute these forms to produce an oral solution or suspension, which can be a complex process (1,2). The advantage of these powders or granules over multidose ready-to-use solutions or suspensions is that they lack certain excipients that are dangerous for children, ordinarily added as humectants, solubilisers or thickeners, such as propylene glycol, ethanol or castor oil. However, the information provided in patient leaflets is often insufficiently clear and detailed to enable a child's carer to successfully and safely complete the complex preparation procedure. We pointed out this problem with the patient leaflet for Isentress° in 2017 (2). The situation has been vastly improved since then by the inclusion of a detailed, illustrated, easy-to-follow booklet of instructions for use in the box, in addition to the patient leaflet.

We noted some other advances for children in 2019, for example: Humira° (*adalimumab*), in pre-filled, fixed-dose syringes and pens, is more convenient for use in children; and some products, such as Orfadin° (*nitisinone*) were made available in oral liquid form. But these improvements were long overdue and opportunistic, appearing only when generic versions of these drugs were about to be permitted on the market. Such improvements may have been made to comply with a paediatric investigation plan agreed between the EMA and the pharmaceutical company several years previously, enabling the company to obtain 6 additional months of market exclusivity for the drug, even for its indications in adults.

In summary

The drug packaging market is improving, but there are also still many examples as of 2020 that pose a danger to patients, in particular children and pregnant women. These flaws affect prescribers, pharmacists and nurses through the complications they cause. Healthcare professionals find themselves in the situation of having to prevent, notice and report these errors, when they could be avoided in large part through regulatory action and by pharmaceutical companies and agencies setting their minds to improving medication safety.

Prescrire's systematic examination of the packaging of several thousand pharmaceutical products over many years shows that, in national marketing authorisation procedures in France, there is little or no compliance with the ANSM's guidelines on proprietary names, labelling and dosing devices. Representatives of the self-medication industry even contested the ANSM's guidelines on safer proprietary names and labelling before France's supreme administrative jurisdiction (Conseil d'Etat). Fortunately, this institution upheld the legality and merit of these guidelines, confirming their validity as standards to be applied (6). Let's hope that such guidelines will in future be introduced into EU law, in order to make them mandatory.

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