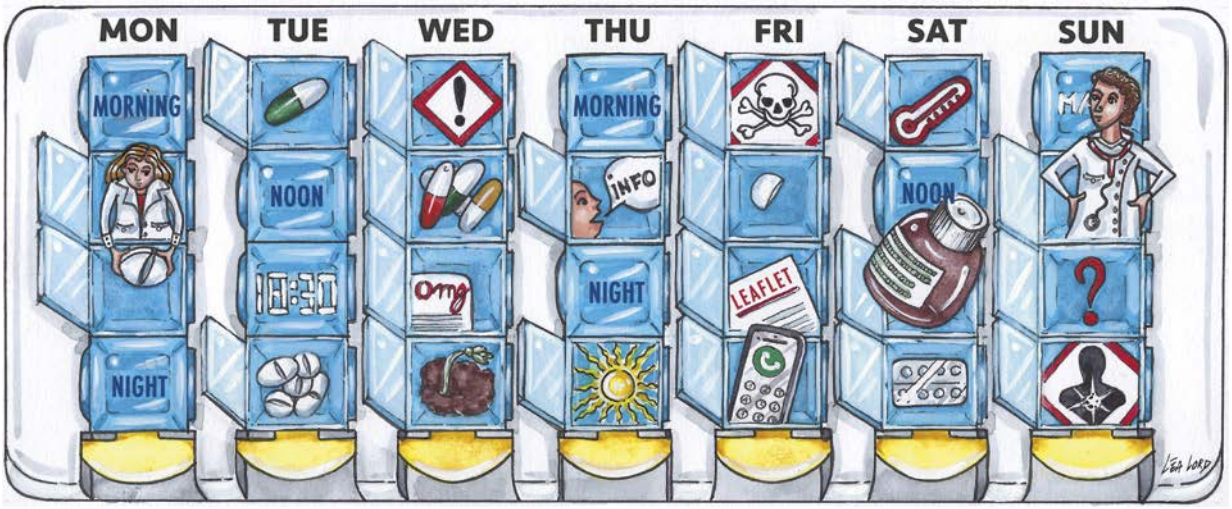


2018 drug packaging review: proposals to reduce the dangers of poor-quality packaging

ABSTRACT

● ***Prescrire*** **examined the packaging quality of 220 products in 2018. The stark conclusion that has emerged from the 7000 packaging analyses we have conducted since 1981 is that most drug packaging fails in its function of ensuring that patients receive the right drug at the right dose in the settings in which they are likely to be used. Flaws include: the drug's real name (its international non-proprietary name or INN) and dose strength being insufficiently legible on the labelling; unit-dose packaging being rare; and information required to protect patients from many high-risk situations missing from the patient leaflet.**

● **In 2018, the French drug regulatory agency ANSM showed that it is finally taking the dangers of sub-standard packaging more seriously, by setting more stringent standards for labelling, including recommending that pharmaceutical companies stop marketing umbrella brands and package their drugs in unit-dose blister packs.**

● **A number of healthcare practices are on the rise: dose preparation, oral chemotherapy in the community, and procedures to prevent or intercept and report medication errors. These practices show the dangers of certain types of packaging.**

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A drug's packaging is a key determinant of its harm-benefit balance. Its primary function is to identify the drug's composition. It should also protect the drug from the environment (heat, humidity and light). It is supposed to reduce the risk of medication errors. It is also supposed to protect patients and health professionals from any toxicity that could result from handling the drug. It should perform these functions at every stage of its distribution and use: during transport, storage, dispensing, dose preparation and administration. Drug packaging also directly informs users about the product, especially its composition, conditions of use, interactions and adverse effects, via labelling and the patient leaflet (1).

The French drug regulatory agency (ANSM) received over 12 000 medication error reports between 2013 and 2017. In 81% of cases, actual medication errors had reached the patient, another 8% involved errors that had been intercepted before drug administration (near miss errors), and 11% were potential errors, deduced from observations indicating potential dangers; 30% of reports were related to labelling (2,3).

Prescrire has analysed the packaging of about 7000 products since 1981, including 220 in 2018. We have identified numerous potential dangers. Our most striking findings are mentioned in the Prescrire Awards, published each year in the February issue of our French edition and in the March issue of *Prescrire International*, as well as in our annual packaging reviews (1).

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French drug regulatory agency recommends improving legibility of INNs on labelling

In 2018, the ANSM finally issued guidelines on the labelling of tablets and capsules (**a**). By supplementing standard legal mechanisms (laws, decrees and orders) with its own guidelines, the ANSM is clearly adopting an increasingly proactive role in promoting good practice in medication use and safety. Although guidelines are optional by their very nature, these recommendations set out the standards the ANSM considers important for patient safety and which it expects manufacturers to take into account.

Safe labelling: industry has a long way to go. The ANSM recommends giving prominence in the labelling of tablets and capsules to the information needed to identify the drug by its international nonproprietary name (INN) and its dose strength, and for traceability (batch number). It therefore recommends perforated unit-dose blister packs as the safest packaging. The overriding aim is to ensure that the right product is administered to the right person. The ANSM strongly encourages manufacturers to tone down other aspects of the labelling that make no contribution to safe medication use, such as trademarks, logos, and promotional graphics that trivialise the harms associated with drugs by depicting plants or fruit, for example.

Will drug labelling get a makeover in 2019? In 2018, as in previous years, we continued to see labelling that failed to give due prominence to the INN, such as: Dicetel° (*pinaverium*), Nocertone° (*oxetorone*), Ginkor Fort° (*Ginkgo biloba* + *heptaminol* + *troxerutin*), Décontractyl° (*mephenesin*), Trolovol° (*penicillamine*) and Androgel° (*testosterone*). The same flaws that reduce the legibility of INNs that *Prescrire* has been describing for years have now also been pointed out by the ANSM: the use of small, fine, low-contrast lettering; overly prominent trademarks and logos; and poorly legible non-unit-dose blister packs. Yet again, one-quarter of the solid oral drugs *Prescrire* examined in 2018 were packaged in bulk bottles, for example: Efferalgan° orodispersible tablets (*paracetamol*), Méthotrexate Bellon° tablets, Ocaliva° (*obeticholic acid*), Procysbi° (*mercaptamine*) and Tivicay° (*dolutegravir*). Other examples were pointed out by reviewers of this article: Purinethol° (*mercaptopurine*), Lanvis° (*tioguanine*), Vesanoïd° (*tretinoin*), Epitomax° (*topiramate*), and many antiretroviral drugs. The list is long. One major problem is that once removed from the bottle, these drugs are no longer identifiable or protected (4).

To ensure that the right drug is administered to the right person:

– The INN and dose strength must be prominently displayed in their entirety and remain legible on the labelling throughout the medication use system, as is the case with Fluoxetine Biogaran°, Kanuma° (*sebelipase alfa*) and Taltz° (*ixekizumab*);

– Drugs must be available in unit-dose blister packs, for example: Emtricitabine + tenofovir disoproxil Mylan°, Kisqali° (*ribociclib*), Ninlaro° (*ixazomib*), Orobupré° (*buprenorphine*), and Zejula° (*niraparib*). With unit-dose blister packs, health professionals can dispense individual doses without having to remove drugs from their original packaging then repackage and label them, and the drugs remain under the storage conditions tested as part of the marketing authorisation process (see inset p. 192).

The ANSM's guideline on labelling and its guideline on the choice of brand names encourage pharmaceutical companies to discontinue "umbrella" brands, which pose too many dangers to patients: a single brand name is shared by several products containing different active ingredients with different harms, and the promotional components of their labelling (similar logos and graphics across the entire product line) increase the risk of confusion by drawing the consumer's attention away from the information about the products' composition (5). However, as of early 2019, these dangers persist due to the continued presence on the French market of many umbrella brands, such as Apaisyl°, Sédermyl°, Humex° and Clarix°.

INNs underused in patient leaflets. European guidelines discourage overuse of a product's invented name in the patient leaflet and encourage the use of terms such as "*this medicine*" or the pronoun "*it*" (6). But all too often, pharmaceutical companies do not apply these rules on the information about the composition of their medications.

Patient leaflets generally start with the brand name then the INN, as the title. Our examination of patient leaflets reveals that this title often gives greater prominence to the trademark. And the trademark is often overused throughout the patient leaflet. For example, the patient leaflet for Femi° (*ethinylestradiol* + *norgestimate*) mentions the trademark about 50 times and the composition in INNs only twice. The patient leaflet for Vimpat° (*lacosamide*) mentions the trademark about 70 times, and the INN around 10 times. The first section of the Femi° patient leaflet does not mention the INNs at all. It is only at the end of the document that the composition of the tablets is clearly stated.

a-*The ANSM guidelines apply to all solid oral forms: tablets, hard capsules, soft capsules, lyophilisates, powders and granules in sachets. For the sake of simplicity, this article only discusses tablets and hard capsules, which between them account for at least half of our packaging analyses every year.*

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Packaging too often ill-suited to dose prepararation

"Dose preparation" means that a patient's doses of medication are prepared in advance and sorted according to their order of administration. It involves removing the drugs from their original packaging, and sometimes repackaging them in a container other than their authorised packaging (**a**). The process can be manual, where doses are inserted into the compartments of a pill organiser for example, or automated, where a machine is used to repackage individual doses into relabelled transparent pouches. It is mainly used for oral solid forms (tablets, capsules), but some automated systems can repackage a variety of pharmaceutical forms, including liquids (1-4).

The health professionals involved in dose preparation are hospital pharmacists and nurses, nurses who care for dependent patients in the community or in residential care, and community pharmacists who prepare treatments for care homes (1-4). Drugs may also be prepared in this way by patients themselves, or their carers.

All health professionals, regardless of whether they perform dose preparation, should be aware of its risks and limitations.

Dose preparation is not suitable in all cases. Given the uncertainties surrounding dose preparation (see below), the first question to address is which patients may benefit from this practice despite the risks. This entails verifying that the pharmaceutical form and the drug concerned are suitable for dose preparation, estimating the drug's shelf life once it is removed from its original packaging, and ruling out dosing schedules that are conditional or variable (e.g. "as needed") and therefore incompatible with advance preparation (1,3). Most drugs are taken every day. With those that are not, such as once-weekly *methotrexate*, the consequences of mistaking them for a daily treatment when preparing a weekly pill organiser could potentially be very serious.

The dangers of non-unit-dose blister packs. In the early 1980s, hospital pharmacists in France spearheaded a call for drug packaging that would enable safe, reliable dose preparation for individual patients, rather than an entire ward (5,6). It is impossible to reliably identify a drug when most are not available in unit-dose packs and so many tablets and capsules look alike. Our drug packaging analyses in the intervening 30-odd years show that most products are not marketed in unit-dose packaging. This has led some health professionals in the community, hospitals and nursing homes to remove drugs from their original packaging and repackage and relabel them in a unit-dose format, and to automate this process.

Removal of drugs from their original packaging: identification and stability issues. The introduction of dose preparation raises several issues (1-3,7). What is the drug's shelf life once removed from its original packaging? How can this shelf life be determined? Are some substances or pharmaceutical forms incompatible with dose preparation? What container should be used when repackaging them? What information should be included on the new label? How many days' worth of treatment can be prepared in advance? Which hygiene rules should be followed? Guidelines exist, but little evaluation has been conducted (1-3). Another issue, beyond the scope of this article, concerns liability if an error occurs.

When drugs are placed in a pill organiser (or relabelled pouches), the new container must offer the same security as the original packaging, by ensuring that the drugs remain identifiable, protected and traceable right up until they are administered to the patient. Additional checks are required for any information added to the new label that was not present on the manufacturer's packaging, such as the patient's name and the time at which the drug should be taken.

Once tablets and capsules are removed from their packaging, exposure to humidity, heat, light and dust may reduce the quantity of active ingredient they contain and generate degradation products, possibly resulting in toxicity or loss of efficacy (2-4). Degradation is not always apparent. Some oral forms are particularly friable or sensitive to humidity, such as effervescent tablets, lyophilisates and orodispersible tablets.

The shelf life of drugs after removal from their original packaging is not generally stated in the summaries of product characteristics (SPCs) or patient leaflets. When questioned about this, the ANSM confirmed that pharmaceutical companies are only required to provide data on the storage conditions of their drugs in their original packaging. According to the European Pharmacopoeia, health authorities should encourage pharmaceutical companies to conduct stability studies on drugs without their immediate packaging. But when such data are not available, drugs should be kept for the shortest possible time outside their original packaging (1). A guideline issued by a French Regional Health Agency recommends preparing no more than 7 days' worth of treatment in advance (2). Other sources recommend a maximum of 10 days to 180 days, depending on the conditions (3,7). These different recommendations reflect the fact that accurate evaluations are lacking.

Risk of cross-contamination. Cross-contamination occurs when particles from unpackaged drugs are deposited along the pathway they take through an automated dose preparation system (hoppers and chutes) before reaching their pouch, and are then transferred onto other drugs that subsequently pass through the system (2). This can also happen with multi-patient pill organisers. Cross-contamination with cytotoxic drugs is particularly dangerous, but contamination with other drugs, such as psychoactive agents, hormones, antibiotics or antivirals can also cause problems, not to mention tablets and capsules being contaminated with potential allergens. Thorough cleaning procedures for automated dose preparation equipment, which should also be applied to pill organisers, and protective measures for operators are recommended (2-4).

Additional information for patients and carers. Patients who receive drugs through dose preparation systems

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require additional information, such as how to use their pill organiser or explanations about the information on relabelled drugs. A general drawback of repackaging is that the drug becomes separated from the patient leaflet, which means that the information it contains is no longer available at the time and place it is most needed. It is advisable to make sure that such patients or their carers have the information they require (8).

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a- *Both removing a drug from its primary packaging (blister, bottle) and repackaging it in a transparent pouch with a new label constitute off-label use because, unlike reconstitution of an oral or injectable suspension for example, neither procedure is described in the summary of product characteristics or was intended when the drug was authorised. It is sometimes possible to repackage a drug without removing its immediate packaging, for example by placing a detached portion of a blister pack in a bag.*

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Unsuitably packaged paediatric drugs

Children continue to be endangered by the practice of failing to adapt a product's formulation and packaging for paediatric use when a product initially intended for adults is subsequently authorised in children.

The indications for *sevelamer* powder for oral suspension (Renvela°) have been extended to include the treatment of children aged 6 years and older, requiring doses of 0.8 g or 1.6 g and the ability to adjust the dose by increments of 0.4 g or 0.8 g respectively, which the SPC states should be measured with a 1-ml measuring scoop or measuring spoon. But in France, as of early 2019, no dosing device is provided with the 2.4 g sachets, the 0.8 g and 1.6 g dose strengths are not available, and a 0.4 g dose strength has not been authorised in the European Union.

Vimpat° syrup (*lacosamide* 10 mg/ml) used to be authorised for use in adults and children weighing more than 50 kg, and the box contained a 30-ml measuring cup. When its indications were extended to include children weighing less than 50 kg, a 10-ml oral delivery syringe was added. As of 2019, the "adult" pack of Vimpat° syrup therefore also serves as the "child" pack, by including two different dosing devices, which could cause confusion. As both devices are graduated in millilitres, users must systematically calculate how many millilitres of syrup to measure in order to administer the number of milligrams prescribed, with a risk of ten-fold dosing errors. Most dosing devices examined by *Prescrire* in 2018 were graduated in millilitres, such as those provided with Celsentri° (*maraviroc*), Kaletra° (*lopinavir* + *ritonavir*) and Tamiflu° (*oseltamivir*).

It would be more prudent to provide a 50 mg dose strength of *hydroxycarbamide* (Siklos°) for children with sickle-cell disease than a 100 mg divisible tablet. This would avoid the risk of cutaneous cytotoxicity and contamination of the environment with debris generated when splitting the tablets. It would also be safer if the labelling made it easier to distinguish between the 100 mg and 1000 mg dose strengths of *hydroxycarbamide*.

The indication for Étiléfrine Serb° (*etilefrine*) in France has been changed from orthostatic hypotension in adults to priapism, which also occurs in children with sickle-cell disease. Its packaging, however, has not changed: the dose strength is inappropriate for children (half of the contents of an ampoule must be withdrawn); no equipment for preparation or injection is supplied; and the patient leaflet contains too little information about self-injection.

As in previous years, several drugs of varying toxicity, mainly oral liquid preparations, were supplied in bulk bottles without a child-proof cap in 2018: Théralène° (*alimemazine*), Mucoplexil° (*carbocisteine*), *fluconazole* products (e.g. Fluconazole Biogaran°), *fluoxetine* products (including Prozac°), Panfurex° (*nifuroxazide*), Efferalgan° orodispersible tablets and Dolko° (*paracetamol*), and A 313° (*vitamin A*). Yet packaging solutions are available to prevent children from tasting or swallowing drugs without their carers' knowledge: bottles of Noyada° (*captopril*), Vimpat° (*lacosamide*) and Triflucan° (*fluconazole*), for example, are equipped with a child-proof cap; Orobupré° (*buprenorphine*) blister packs are covered with a child-proof film; and boxes can incorporate a safety catch, such as the one used for Galafold° (*migalastat*).

Handling oral antineoplastics in the home: the dangers should be taken more seriously

A new programme is due to be introduced in France in 2019, whereby community pharmacists will receive payments from the national health insurance system

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to provide support for cancer patients treated with oral chemotherapy at home (7).

Oral antineoplastics are less problematic to prepare and handle than injectable forms, for which very strict precautions apply in the hospital setting (**b**). The toxicity of these drugs, their increasing use at home, and their complex, substandard packaging must be taken into account, particularly when used by persons unfamiliar with handling them (8).

Inform patients, improve patient leaflets. The preparation of injectable cytotoxic antineoplastics carries a high level of risk, requiring stringent measures to prevent direct skin contact, inhalation, and contamination of the environment. Studies have shown the presence of antineoplastics in the urine of exposed pharmacists and nurses (8). In the community, pharmacists, nurses, patients and their carers would do well to apply the following measures when handling these drugs:

– Women who are or could become pregnant or are breastfeeding should not prepare doses;
– Gloves should be worn;
– Preparation area should be contained;
– Warning signs should be used when someone is preparing the drug, to ensure that they are not disturbed;
– Waste generation and disposal must be planned to prevent contamination of the environment: in particular, drugs should be removed from their immediate packaging and tablets split over a disposable paper tissue, and volumes of oral liquid preparations such as *mercaptopurine* suspension should be measured over a disposable absorbent leak-proof pad, such as a bed protector, etc.;
– Excreta containing cytotoxic residues (vomit, stool, urine) must be carefully managed. If no specific ecological waste disposal system is in place, they could be collected in a stainless-steel container and disposed of in the toilet (8).

Cyclophosphamide is excreted through sweat, which requires certain precautions, such as washing the patient's clothes separately (8).

This advice is not new, but it is rarely mentioned in patient leaflets. Brief instructions on handling the drug are included in some patient leaflets (e.g. Siklos° (*hydroxycarbamide*)), but not in others (e.g. Novatrex° (*methotrexate*)).

Variously and sometimes dangerously packaged antineoplastics. The French drug database Thériaque (www.theriaque.org) includes about 70 antineoplastics marketed in bulk bottles. Bulk bottles carry a higher risk of contamination, and patients are more likely to lose a tablet without realising it. Blister packs, preferably unit-dose blister packs, are better choices. Among the products we examined in 2018, Novatrex° (*methotrexate*) in blister packs is a better choice than Méthotrexate Bellon° in a bulk bottle with no child-proof cap. None of the antineoplastics marketed in blister packs that we examined in 2018 had a child-proof film, and none of the boxes had a safety catch to prevent accidental ingestion by a child.

In addition, antineoplastics that require gradual titration (e.g. *venetoclax* (Venclyxto°)) or tapering to manage adverse effects (e.g. *ribociclib* (Kisqali°)) can require complex dosing schedules. Health professionals must check that patients have understood them. This complexity sometimes carries over to the packaging, with multiple dose strengths and unusual formats.

In practice Overcoming packaging flaws

Health professionals involved in the various stages of medication use (prescribing, dispensing, dose preparation, administration and treatment monitoring) are well placed to notice potential dangers and errors related to substandard packaging, and to report them to pharmacovigilance authorities. To help health professionals anticipate these risks and better protect patients, the European Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that packaging mock-ups be made available in the annexes of marketing authorisation applications (1). As of early 2019, neither the ANSM nor the European Medicines Agency (EMA) has implemented this recommendation.

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b- *The dangers associated with handling older cytotoxic drugs are relatively well known. But according to the US Centers for Disease Control and Prevention (CDC), many other drugs should be regarded as hazardous, including abiraterone, sunitinib and vemurafenib, as well as other drugs with carcinogenic, mutagenic, fetotoxic or teratogenic properties, or that are toxic at low doses. Examples include alitretinoin, azathioprine, colchicine and finasteride (ref 9).*

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