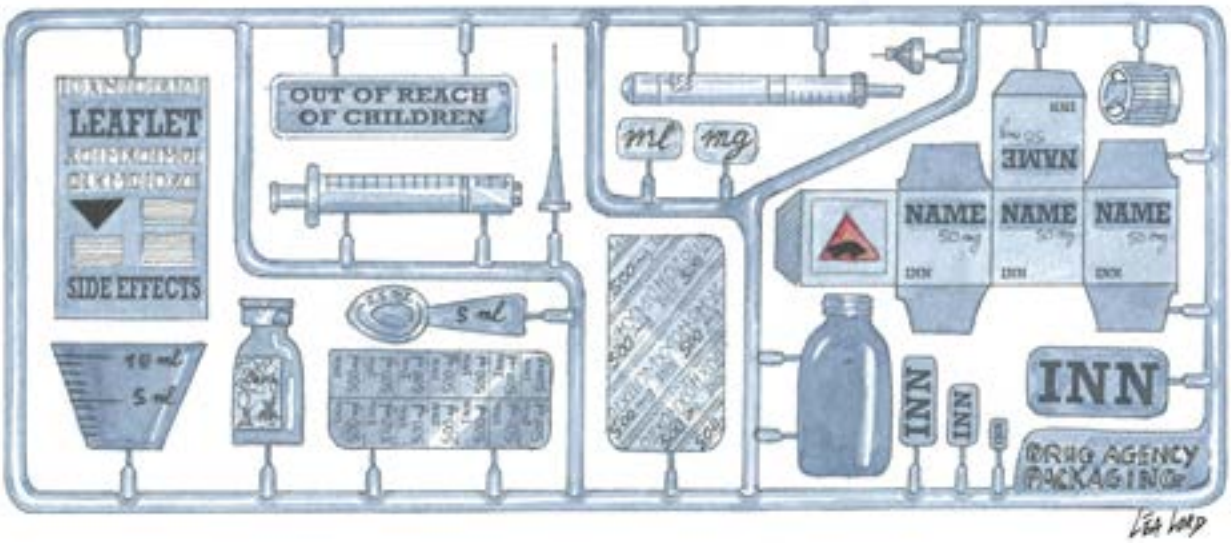

Drug packaging in 2016: marketing takes precedence over public health

ABSTRACT

● ***Prescrire*** **examined the packaging quality of about 250 drugs in 2016. As in previous years, our analyses identified numerous flaws liable to cause medication errors, some of which could have serious consequences, such as labelling geared more towards marketing the product than ensuring medication safety, inaccurate or even dangerous dosing devices, toxic drugs marketed in bottles without a child-proof cap, and patient leaflets that fail to clearly and fully inform patients about adverse effects.**

● **One labelling flaw that has persisted for decades is the insufficient prominence given to the drug's real name, its international nonproprietary name (INN). As a result, patients have difficulty identifying the composition of their medication, with all the risks this entails.**

● **Umbrella brands constitute a particularly shocking example of this problem, creating a risk of confusion between drugs with different compositions marketed under the same brand name.**

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In 2016, *Prescrire* examined the packaging of about 250 drugs available on the French and European markets, some for new drugs and some for older drugs. Ease of use is an important aspect of a drug's harm-benefit balance. A drug's packaging must enable it to be used correctly and safely, in every situation. Well-designed packaging can sometimes constitute a therapeutic advance. However, *Prescrire*'s analyses of the packaging of thousands of drugs reveal the same disturbing situation year after year: many technical solutions are available for providing high-quality packaging, but they are rarely implemented. These solutions are not sufficiently imposed on pharmaceutical companies by regulations and regulatory agencies, and, as a result, many drugs are marketed in poor-quality and sometimes dangerous packaging.

What dangers did we identify through our packaging analyses in 2016? Were there any positive developments?

Unsafe packaging liable to result in errors and adverse effects

The main features of high-quality packaging are:
– The drug is ready to use;
– Each dose is individually packaged and labelled;
– The international nonproprietary name (INN) of each active ingredient is prominently displayed on the box and primary packaging (i.e. blister pack, bottle, sachet, etc.);

– Other information useful for preventing harm is clearly legible: dose strength, route of administration, storage conditions;
– The dosing device is appropriate and accurate;
– The drug can be easily distinguished from other drugs within the same product line;
– The patient leaflet is clear, legible and informative, especially with regard to risks;
– Child-proofing measures are taken to prevent accidental ingestion by children (1).

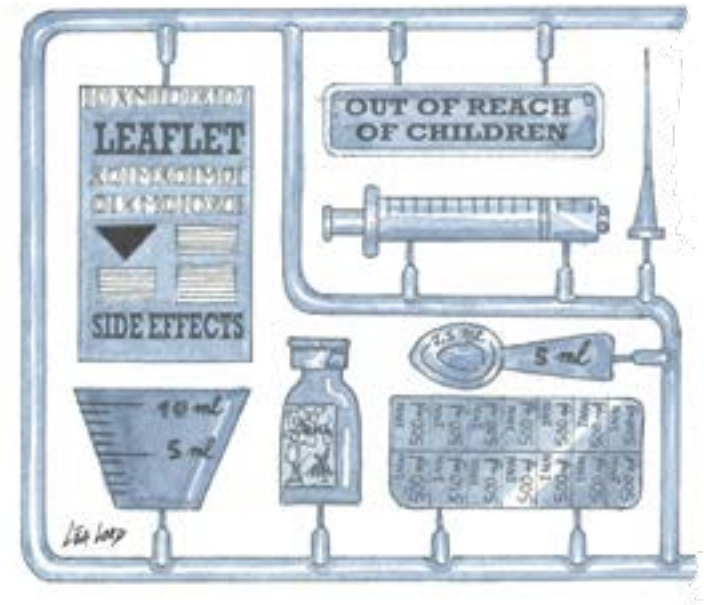
The best and the worst examples of drug packaging were yet again in evidence for the drugs available on the French or European market in 2016.

Injectable drugs: sometimes difficult to use. Some injectable drugs are ready to use or easy to reconstitute, such as influenza vaccines in pre-filled syringes, *dulaglutide* (Trulicity°), and *follitropin alfa* (Ovaleap°).

Other injectable drugs are more difficult to use, however. Some drugs require reconstitution before administration, such as *carfilzomib* (Kyprolis°); or dilution, such as *nivolumab* (Opdivo°); or both, such as the first version of Keytruda° (*pembrolizumab*). Each step creates opportunities for error. The once-weekly *exenatide* pen (Bydureon°) is ready to use but must be tapped up to 80 times to thoroughly mix the powder and solvent before administration.

Some drugs intended for self-injection, such as Progiron° (*progesterone*), are supplied without a syringe or needle.

Unit-dose blister packs: too rare in community pharmacies. Unit-dose blister packs, where each perforated blister pocket is labelled with the INN and dose strength, such as Neofordex° (*dexamethasone*) or Sivextro° (*tedizolid*), are among the clearest, safest, most convenient forms of primary packaging. But in France very few drugs were packaged in this way in 2016, especially drugs supplied through community pharmacies. Some drugs are available in French hospitals in unit-dose blister packs, but are provided in lower-quality blister packs in the community, e.g. Brintellix° (*vortioxetine*) and Doliprane° (*paracetamol*).



With lower-quality blister packs, if a dose needs to be detached for subsequent administration, the detached portion of the blister pack rarely displays all the information required for safe dosing, in particular the INN and dose strength. To cite just one example among many: the full details are only printed 2 or 3 times across a French blister pack containing 15 tablets of *enalapril* + *lercanidipine* (Lercapress°). Sometimes, these details are printed in a way that could be misinterpreted. For example, the French blister packs of *vortioxetine* (Brintellix°) available in community pharmacies are divided into perforated sections labelled with the INN and the dose strength. But each detachable section contains two tablets rather than one, so that in practice, users cannot be sure whether the dose indicated is contained in one or two tablets.

Too many medications supplied in bulk bottles. European health authorities too often accept very poor-quality packaging, such as bulk bottles of tablets or capsules. The main risks associated with this type of primary packaging are that the drug is unprotected when removed from the bottle and that children in particular could ingest a massive overdose, especially if the bottle lacks a child-proof cap. More drugs are supplied in bulk bottles every year, including new antineoplastics, such as *ibrutinib* (Imbruvica°), *olaparib* (Lynparza°) and *trametinib* (Mekinist°). Why are they not supplied in high-quality primary packaging, and in particular in unit-dose blister packs, which are clearer, safer and more practical?

Children are particularly at risk. As we have already observed in previous years, many of the dosing devices we examined in 2016 were based on old designs, were mass-produced, and often of poor quality (spoons, cups or droppers). The French Health Products Agency (ANSM) has recognised the need for improvement. Oral liquid pharmaceutical forms are often used for children, placing them at particular risk from dosing devices.

We identified no advances in 2016 to protect children from the risk of drug poisoning. Oral solutions and syrups containing *codeine* are a prime example of how little attention is paid to this risk. None of the 13 bottles available in community pharmacies in France had a child-proof cap. Yet the fact that bottles of *amoxicillin*, *ibuprofen* or *paracetamol* costing about 2 euros have such caps proves that they add little to the price of the product.

In 2016, Europe's Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) unfortunately decided not to draw up a European list of medications for which a child-proof cap would be mandatory, deeming it sufficient to require that boxes display the statement "*Keep out of sight and reach of children*" (2).

Sharing information about medication errors: major scientific benefits

Poorly designed packaging is dangerous. Analysis of packaging-related medication errors, such as dose preparation or administration errors, makes it possible to take action to minimise the risks in future. And sharing knowledge about factors that contribute to these errors is educational for health professionals (3). But these errors are too rarely reported to drug regulatory agencies, and reviews of reported medication errors are too rarely published.

A few examples of packaging-related errors were reported in *Prescrire* in 2016.

A few packaging-related errors. A French team investigated the large number of preparation errors that have occurred with two older and frequently used oral liquid antibiotics: Clamoxyl° containing *amoxicillin* and Josacine° containing *josamycin*. The errors were caused by difficulty in obtaining a homogeneous suspension or understanding either how much water to add or the graduations on the spoon.

A patient reported an allergic reaction with Lysopaïne° containing *cetylpyridinium* + *lysozyme* to a community pharmacist. The pharmacist discovered that the culprit drug was actually Lysopaïne° containing *ambroxol*, illustrating the danger of umbrella branding, where drugs with different compositions are marketed under the same brand name.

Preparation and handling errors with *leuprorelin* (Eligard°) have led to lack of efficacy. The patient leaflet has been clarified, but the promised modification of the dosing device has yet to materialise in France.

A 3-year-old child died of a *tramadol* overdose because a Doliprane° (*paracetamol*) pipette was used to prepare the dose. Other, sometimes fatal, *tramadol* overdoses have been reported in children, in particular due to confusion between the number of drops per dose and the number of drops per kg of the child's body weight (4-6).

Overdoses have also been reported with *levetiracetam* (Keppra°) oral solutions, mainly due to errors in the use of the dosing devices. The European Pharmacovigilance Risk Assessment Committee (PRAC) reported these overdoses in January 2016, but the European Medicines Agency (EMA) and ANSM have still not published their detailed analysis on the causes.

Brand names: prominently displayed on labelling for promotional purposes, at the expense of INNs

In the European Union, pharmaceutical companies have the option of giving their medicinal products a brand name, which can be either an invented name, such as Azopt°, or the INN followed by the company's name or a trademark, for example Brinzolamide EG° (a generic version of Azopt°).

European regulations state that boxes and the primary packaging must first display the brand name, followed by the dose strength, the pharmaceutical form and, if appropriate, the intended patient population (adults, children, infants), then the INN. Drug regulatory agencies have also issued guidelines on labelling quality (**a**)(7). In particular, a European recommendation stresses the importance of affording due prominence to the INN for safety reasons (8). But too often, this recommendation is ignored.

Invented names: pure marketing. A widespread practice is to give the most prominence to the invented name on labelling through the use of large, bold lettering, bright colours, unusual typography, etc. In contrast, the INN is printed in small, fine, plain characters, and rarely in colour.

The INN is often overshadowed by other promotional features in addition to the invented name. To continue with the example of Azopt°, the Alcon logo (three A letters), displayed on other drugs marketed by this pharmaceutical company, occupies half of the front of the box. The other most prominent features on the labelling are the names "Azopt°" and "Alcon". In contrast, the most prominently displayed information on boxes of Brinzolamide EG° is the INN.

INN: a drug's real name. INNs contain a stem that often conveys information about the drug's mechanism, its origin, its chemical or biochemical affiliation and its therapeutic class. This information usually provides clues about the drug's adverse effect profile. In contrast, invented names are not designed to inform users about the drug's harms, but rather for marketing purposes, to be easily remembered with the aim of increasing sales.

For example, *tianeptine* has been marketed in France since 1988 under the invented name Stablon°, a word that suggests "stability", which for an antidepressant suggests efficacy. However, its INN *tianeptine* shows that it is related to *amineptine*, a drug now withdrawn from the French market, with which it shares similar serious hepatic, neuropsychiatric and cutaneous adverse effects. Under the circumstances, it is not surprising that the company has chosen to afford greater prominence to the invented name than to the INN on the box.

Another example among the French packaging examined in 2016: two topical *tretinoin*-containing products, Érylik° and Kétrel°. *Tretinoin* must not be used by women who are or could become pregnant, because it is teratogenic. For safety reasons, the

a- *Prescrire has criticised the recommendations on brand names issued by the EMA, for not putting sufficient emphasis on patient safety, as well as those issued more recently by the ANSM, which legitimise haphazard labelling and maintain umbrella branding for drugs, thus placing patients at risk. Prescrire has also warned of the dangers of expressing dose strength and concentration on drug labelling in the terms used for administrative purposes rather than in terms that would prevent medication errors (refs 9,15).*

labelling on the boxes and tubes should bear a conspicuous warning about the presence of *tretinoin*. Unfortunately the reverse is true: the INNs are printed in fine grey characters, 7 times smaller than those used for the brand names.

In summary, instead of being considered as the most important information provided on the labelling, the INN is mainly given prominence by companies that market generic drugs. In other situations, the invented name usually takes precedence over the INN, despite the European recommendation to afford due prominence to INNs.

Disparities in the prominence afforded to INNs. According to our analyses in 2016, INNs are relatively prominent on the boxes of drugs authorised through the centralised procedure (signed by the European Commission on the EMA's recommendation); they are also distinguished from brand names by the use of bold characters or colour.

INNs are much less visible, however, on the labelling of drugs authorised through exclusively national procedures, which in France are under the control of the ANSM. Examples among the drugs examined by *Prescrire* in 2016 are *mizolastine* (Mizocler°), *tramadol* (Contramal°) and *codeine + ethylmorphine* (Tussipax°). Yet European rules also apply to national marketing authorisation procedures.

In addition, the ANSM allows multi-term brand names that include all manner of details about the drug, including its INN, pharmaceutical form, flavouring and the clinical situation, symptoms or age group for which it is intended, a practice that is particularly prevalent in drugs used for self-medication (7). The labelling of these drugs is also haphazard, with prominence given to unimportant terms but rarely to the INN. Nowhere is this more evident than in the packaging of umbrella brands.

Umbrella branding: confusion. In umbrella brands, a variety of products with different uses and containing different active ingredients are sold under a single brand name, with the aim of building brand awareness. As a result, a brand name such as Drill°, Fervex°, Humex° or Lysopaïne° can correspond to several INNs. On the labelling, the INN is barely afforded more prominence than the drug's flavour, for example. And the brand name overshadows all the other information printed on the boxes.

The strong visual resemblance between the various products within the same umbrella brand exposes patients to the risk of wrong-drug errors. For example, by taking "Fervex°", a pregnant woman could be exposing her unborn child to the harmful effects of the vasoconstrictor *pseudoephedrine*, or a vehicle driver or machine operator could be subjected to the sedative effects of an antihistamine.

In 2016, the ANSM released some proposed national recommendations on brand names for public consultation, including a section on umbrella brands (7,9). Unfortunately, the ANSM proposes to regulate the naming of umbrella brands rather than simply banning them, which would be the safest way forward for patients. The ANSM only plans on prohibiting the inclusion of products with different statuses (drugs, dietary supplements or medical devices) within the same umbrella brand (7).

Adverse effects in patient leaflets: recurrent shortcomings

The purpose of the patient leaflet is to provide patients with information about their medication. One of the annexes to the marketing authorisation issued by the authorities defines the information the leaflet must contain. But the level of information provided, its clarity and the frequency with which it is updated mainly depend on the summary of product characteristics (SPC) with which it must comply. Every year, *Prescrire* finds that known harms are omitted from the SPCs and patient leaflets of both new and older drugs. Here are a few examples identified in 2016.

Insufficient prioritisation of adverse effects. When marketing authorisation is first granted, the adverse effects stated in the SPC are based on the clinical trial data the pharmaceutical company considered worth mentioning, and on the regulatory agency's analysis of these data. However, clinical trials are rarely designed to determine a drug's adverse effect profile, which means that it is often poorly evaluated at the time of market introduction (10). Ultimately, few adverse effects are mentioned in the first version of the SPC and patient leaflet for a new drug (11). Uncertain harms are not always clearly stated.

One example of insufficient prioritisation of adverse effects in SPCs and patient leaflets is *idebenone* (Raxone°), authorised in the EU for the treatment of a rare form of optic neuropathy. It was evaluated in only a few hundred patients. Since two cases of serious liver injury potentially linked to *idebenone* had already occurred during its clinical evaluation, this risk warrants particular attention. The adverse effects section of the SPC for Raxone° mentions its most frequent effects first: diarrhoea, nasopharyngitis, cough and back pain. Other adverse effects are listed in a table, including various hepatobiliary laboratory disturbances, followed by "*hepatitis*" (without mentioning its severity).

The patient leaflet lists all of the adverse effects mentioned in the SPC, with no further details, in descending order of frequency. In 10th place on the list of 14 is the rather convoluted statement "*high levels of some liver enzymes in the body which mean you have liver problems – shown in tests, high levels of "bilirubin" – this can make your skin and the whites of your eyes look yellow, hepatitis*".

The inverted black triangle is present on the patient leaflet. It is a symbol that must be displayed in the European Union on the patient leaflets of drugs subject to additional monitoring, without specifying that the hepatotoxicity of *idebenone* is being monitored as part of a risk management plan (RMP).

Omissions and failure to update the documentation of older drugs. In 2015, we gave a Red Card to the patient leaflets for vaginal drugs containing *estriol* available in France (all authorised through national procedures about 20 years ago), because they do not provide sufficient information about the risk of arterial or venous thrombosis and breast or endometrial cancer. As of 2016, these patient leaflets have still not been updated. Yet these harms have been clearly established and are mentioned in the patient leaflet for Estring°, a vaginal ring containing *estradiol*, recently authorised through a European decentralised procedure (12).

The patient leaflets for the cutaneous retinoids available in France, *adapalene*, *alitretinoin*, *isotretinoin*, *tretinoin* and *tazarotene* advise against or contraindicate their use during pregnancy, but lack full and harmonised information about the risks of teratogenicity. Most of them fail to mention the need for effective contraception (13).

The patient leaflets for drugs authorised through European procedures are generally more informative than those for older drugs approved through the French national procedure, which are no longer or rarely updated after a certain period of time (13). Shortcomings are also to be found in European patient leaflets. For example, as of late 2016, the SPC and patient leaflet for *prucalopride* (Resolor°) contain no mention of the three cases of suicidal ideation linked to *prucalopride* reported by the WHO in patients with no prior psychiatric history (11).

Lists of adverse effects need to be clearer and more informative. When a drug has many known adverse effects, the length of the list can discourage patients from reading about adverse effects, and as a result, the most troubling effects may go unnoticed. Some leaflets help patients understand the risks posed by their medication, by discussing the most serious adverse effects first, then listing the others in descending order of frequency, such as in the patient leaflets for *ibrutinib* (Imbruvica°), *ponatinib* (Iclusig°) and *lenalidomide* (Revlimid°) (11).

Often these long lists do not seem to be written to provide information to patients, but rather to protect pharmaceutical companies from litigation, since the company cannot be held liable for harm caused by a defect in their drug if the adverse effect was mentioned in the patient leaflet. This is one of several obstacles encountered by victims of drug-induced harms (14).

Choosing to protect patients

Drug packaging plays an important role in ensuring that drugs are used correctly and in preventing adverse effects. Options that improve patient safety are not sufficiently imposed on pharmaceutical companies by drug regulatory agencies. Regulators too often put patients at risk by authorising drugs with substandard packaging. And pharmaceutical companies still too often tend to give prominence to marketing features on drug labelling and too little prominence to information that is useful for healthcare, such as the INN, and endanger patients by underestimating the important role of packaging.

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

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