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Two issues are especially worrisome. First, packaging too often poses a danger to children. In addition, too many patient leaflets provide incomplete information about adverse effects, thus failing to properly protect the most vulnerable patients.

Yet, the method Prescrire used to analyse drug packaging shows that it is not difficult to detect and anticipate risks. It is up to healthcare professionals to take advantage of the method, to protect patients from, and report, dangerous packaging.

**Abstract**

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- Two issues are especially worrisome. First, packaging too often poses a danger to children. In addition, too many patient leaflets provide incomplete information about adverse effects, thus failing to properly protect the most vulnerable patients.
- Yet, the method Prescrire used to analyse drug packaging shows that it is not difficult to detect and anticipate risks. It is up to healthcare professionals to take advantage of the method, to protect patients from, and report, dangerous packaging.

In 2012, children appear to be the population group most overlooked in the marketing authorisation process, in terms of packaging (2).

**Think about children first**

Are drug regulatory agencies and pharmaceutical companies concerned about children accidentally or erroneously exposed to drugs intended for adults? The situation is common, since medicines are present in almost every household.

Various examples identified in 2012 illustrate the extent of the problem.

No child-proof cap: poisonings, accidents. The risk of accidental ingestion of caustic household products, such as hydrochloric acid or sodium hydroxide, by children is well known (3). But the need to protect children from drug toxicity seems to have escaped the attention of health authorities, given the quantity of drug bottles on the market that lack a child-proof cap (1,2).

Some examples of bottles without a child-proof cap in 2012: Preterval® (perindopril + indapamide), Predyl® (povidone-iodine), and Codotussyl toux sèche® (pentoxyverine).

Paracetamol overdose provokes serious or even fatal hepatic disorders. A retrospective study has shown that the orodispersible form of paracetamol tablets in particular exposes children to a risk of overdose (Prescrire Int n° 132). Yet in 2012, bulk tubes containing a total of 8 g of orodispersible paracetamol were available for self-medication in France without a child-proof cap (Elferalganodis®). These pleasantly tart, fruit-flavoured, effervescent tablets resemble mint candies. This product represents a danger to children and should be withdrawn from pharmacies.

Improvement is possible, however: Paratabs® contains 6 g of orodispersible paracetamol in child-resistant blister packs (a).

Blisters packs that are too easily opened. Other dangerous drugs are marketed in blister packs covered with a film that is easily peeled off, such as Suboxone® sublingual tablets containing 2 mg or 8 mg of the opioid buprenorphine combined with naloxone (Rev Prescrire n° 342). And the tablets give off a lemon aroma when they are removed from the blister pack.

Beware of alcohol. The use of alcohol-based hand sanitisers is now widespread. Accidental ingestion of these products by children has resulted in acute poisoning, with inebriation, agitation, drowsiness and impaired consciousness (Prescrire Int n° 129). Although they are not drugs, cases of this type show that more thought must be given to the risks to which children are exposed due to the presence of alcohol and to excipients used in drug formulations.
Children are particularly vulnerable to errors. In 2012, French poison control centres published a study that identified, over a 2-month period, 169 reports of administration errors involving single-dose containers: 79% of the victims were children under 5 years of age. In 151 cases, the confusion was linked to the victims being containers: 79% of involving single-dose administration errors period, 169 reports of tres published a study that French poison control cen- vulnerable to errors.

The consequences of accidental injection of adrenaline via autoinjectors have sometimes been serious, including finger amputa- tion and death (Prescrire Int n° 131). Several reports concerned children.

The recommended dosage for Flixi- vate® (fluticasone cream and ointment) is one cutaneous application per day (Rev Prescrire n° 341). Yet the dosing schedule on the packaging shows 2 boxes, labelled “morning” and “evening”, implying that it should be applied twice daily, thus exposing infants aged between 3 months and 1 year to the adverse effects of an overdose of a high-potency topical corticosteroid.

European Paediatric Regulation: mainly benefiting the drug industry. In 2012, five years after the European Paediatric Regulation came into effect, the European Commission opened a public debate on its impact (b), giving Prescrire the opportunity to share its conclusions that the results have been disappointing. This Regulation benefits pharmaceutical companies, while children have gained little (2,4).

In March 2011, we evaluated Cozaar® (losartan oral suspension), an expensive product with dangerous packaging, for which the pharmaceutical company did not request reimbursement (Rev Prescrire n° 329). And yet this earned the company, MSD, a 6-month extension for its market monopoly on the drug, including the formulations intended for adults.

Another notable example in 2012: the European marketing authorisation (MA) for Revatio® (sildenafil) was extended in May 2011 to include children aged 1 year or older with pulmonary arterial hyper- tension (Prescrire Int n° 129). In France, however, the paediatric form was not marketed until 17 months later (5). In the meantime, pharmacists had to prepare oral suspensions from tablets for adults using a 14-step procedure, or from the powder form of the drug, and then pack- age these suspensions in bottles. This tricky preparation process added a risk of dosing errors for a drug that can be fatal to children (6).

Prescrire’s packaging analysis

A drug’s packaging refers to all of the items that either protect it until its administra- tion or provide information useful for patient care: the drug’s name (INN), infor- mation on dosing, drug interactions, adverse effects, preparation and adminis- tration, storage (1). It must help to prevent medication errors and accidental ingestion by children. Packaging is therefore an important component of a drug’s harm- benefit balance.

Over 5000 analyses in 30 years. Prescrire analyses the packaging of the new drugs evaluated in the “New Products” section of its French edition, la revue Prescrire.

It also re-examines the packaging of existing products when changes are intro- duced: name change, different dosing device, usage broadened to include vul- nerable patients (children, pregnant women, patients with renal impairment), major new data on adverse effects, etc. Prescrire’s Packaging Working Group then checks whether any item of the packaging is more dangerous as a result of these changes: is the INN harder to read, the closure too weak or the dosing device dan- gerous or unsuitable? And is the informa- tion about pregnancy ambiguous or has information about adverse effects been omitted?

2012: let’s remain vigilant to the risks

Too little progress was observed in 2012. Yet examples of suitable packaging are already on the market. This demonstrates that advances are not necessarily adopted in the field of packaging, and that drug companies are neither sufficiently motivated nor required to do better.

Minor improvements. In 2012, only minor advances were made in terms of packaging: the Pegasy® (peginterferon alfa-2a) ready-to-use pen with a needle shield that conceals and protects the nee- dle; and the Avonex® “Pen® (interferon beta-1a) pen as an alternative to pre- filled syringes.

There were improve- ments in the packaging of some drugs, but they were not sufficient to prevent all of the identi- fied risks. For example, the oral rotavirus vaccine Rotarix® is now ready to use, but the oral applicator still resembles a syringe for injection. It is possible to force a needle onto it and inject the vaccine by mistake.

The quinine + crataegus (dry hawthorn extract) combination Okimus®, market- ed for the treatment of cramps, is now packaged in blister packs instead of bulk bottles. This improvement does not jus- tify keeping it on the market, given its unfavourable harm-benefit balance.

Child-proof caps have been added to the bottles of Uvestérol® D and Uvestérol® ADEC vitamin solutions, but the announced change to the formulation of these solutions has yet to...

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* Child-resistant blister packs are covered with a strong film that is difficult to break without a sharp object. To remove the tablet, the pre-cut blister pocket must first be detached from the strip, freeing an unbroken corona of film which can then be lifted in order to peel off the safety film.

** In 2012, the European Medicines Agency conducted a public consultation on draft guidelines on the development of paediatric drugs, the packaging component of which was grossly inadequate. Prescrire participated in this consulta- tion by offering 20 constructive proposals on improving the evaluation, quality and supervision of packaging to make it safer for children, including a major evaluation at the European level of the risks associated with exipients (ref 2).
2012 drug packaging review

More patient leaflets examined this year provided incomplete information about adverse effects (d).

In 2012, the oral delivery syringe supplied with Ostram® contained a single-dose container of pseudoephedrine, which simply mentions that the maximum daily dose of pseudoephedrine is 240 mg and 480 mg (quetiapine), Xarelto® (rivaroxaban), and Zeboral® (venus-rafenib).

As in previous years, most packaging examined emphasised the brand name, using large, bold type, while the INNs were displayed in small, light-face type without sufficient background contrast. They are sometimes so stylised as to be barely legible, for example on the box for Aldilax® (spiranolactone + furosemide) (e). Again in 2012, some drugs were authorised for sale despite the absence of the INN on packaging items such as the single-dose containers of Saflutan® (tafluprost) and the blister packs of Gélutrophyl® (thienoic acid).

Resemblances between dose strengths, umbrella brands: danger!

In 2012, the packaging of too many different dose strengths from the same product line looked so similar that it could be a source of confusion for users: for example, Xeroquel® extended-release 300 mg and 400 mg (quetiapine), Xarelto® 15 mg and 20 mg (rivaroxaban), and Sycrest® 5 mg and 10 mg (asenapine).

Even more troubling, the French health products agency (ANSM) took no steps in 2012 to ban or strongly recommend against the use of umbrella brands. This practice has become widespread in the self-medication sector: different drugs with different indications and adverse effect profiles are sold under similar brand names, in packaging that often looks very similar (for example, under the umbrella brand Advil®: RhinAdvil® (ibuprofen + pseudoephedrine) (Rev Prescrire n° 345) (7).

Dosing devices: bad habits persist.

In 2012, the oral delivery syringe supplied with OxyNorm® 10 mg/ml (oxycodeone oral solution) combines the major known flaws of dosing devices: it is graduated in millilitres instead of milligrams, creating a risk of confusion between the two units of measurement; there is no graduation for the 2.5 mg dose indicated in the summary of product characteristics (SPC) for patients with renal impairment; and its capacity is too large for the preparation of low doses (1 mg or 2 mg).

Incomplete patient leaflets: dangerous for patients

More patient leaflets examined this year provided incomplete information about adverse effects (d).

In 2012, the box for Ostram® contained a calcium phosphate salt, while equivalent products containing calcium carbonate salts are not contraindicated in these patients.

NSAIDs: patient leaflets should clearly deter their use throughout pregnancy. The patient leaflet for AleveTab® (naproxen) states that (our translation) “during the first 5 months of your pregnancy, your doctor may prescribe this medication, if necessary” (14).

Some information provided in the leaflet for patient leaflets for RhinAdvil® and Rhinureflex® (ibuprofen + pseudoephedrine), although not incorrect, is convoluted and ambiguous, and leaves the door open to the use of NSAIDs during pregnancy depending on “the opinion of your doctor or pharmacist” (our translation) (15, 16).

Exposure to NSAIDs in early pregnancy carries a documented risk of spontaneous abortion. A risk of fetal malformations cannot be ruled out (Rev Prescrire n° 341). There is solid evidence that prenatal exposure to NSAIDs during the second and third trimesters of pregnancy poses a risk of premature closure of the ductus arteriosus, pulmonary arterial hypertension and renal failure. In addition, low-level evidence concerning pseudoephedrine is consistent and points to an increased risk of teratogenesis (Rev Prescrire n° 248).

NSAIDs should never be used during pregnancy: patient leaflets for NSAIDs that do not state this clearly pose a risk to the unborn child, and the risk increases when the NSAID is combined with pseudoephedrine.

In summary. Healthcare professionals can play a role in improving drug packaging by reporting any identified errors, suspected risks and observed flaws: poorly legible INNs, unsuitable dosing devices,
etc. (e). They should choose medicines with the best packaging, advise patients on their use (helping them to identify the INN on labelling, explaining the use of dosing devices), and inform patients about adverse effects that have been omitted from the packaging.

With innovation in new drugs or new indications at a standstill, we could at least expect improvements in the packaging of existing drugs. The pharmaceutical industry and drug regulatory agencies have a duty to embark upon a major packaging safety programme to improve existing packaging, paying particular attention to children and other vulnerable patients. This includes improving the quality of paediatric packaging, banning bottles without a child-proof cap, testing the various models of child-proof caps, requiring child-resistant blister packs for particularly dangerous drugs, improving information about overdose in SPCs and encouraging studies by poison control centres on unintentional poisoning.

It is equally urgent that drug regulatory agencies and especially agency rapporteurs responsible for evaluating marketing authorisation applications should anticipate the inherent risks of the proposed packaging and the risk of medication errors before marketing authorisations are granted.

How many years, accidents and deaths will it take before health authorities recognise the importance of drug packaging and take appropriate action?

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### Selected references from Prescrire’s literature search.

5. ANSM “Revatio poudre pour suspension buvable” 26 October 2012: 1 page.

### Medicines in Europe

See also Prescrire's response to an EMA consultation on potential medication errors: “Safety and usability of packaging and labelling: assessment is required prior to marketing authorisation for all medicinal products, not just for copies of existing drugs (November 2012)”.

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### Coming soon...

**New Products**

- Exenatide combined with insulin
- Eplerenone and chronic heart failure
- Pazopanib

**Adverse Effects**

- Calcium supplementation: cardiovascular risk?
- Tetrazaepam
- Voriconazole
- Leflunomide

**Reviews**

- Bleeding with dabigatran, rivaroxaban and apixaban
- Severe COPD: oxygen prolongs survival

**Outlook**

- Drug companies’ influence starts at university
- Pharmacogenetics and personalised medicine: a critical approach is needed

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