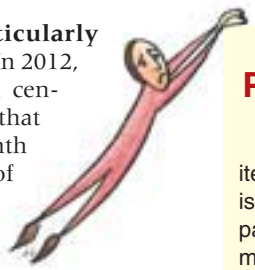

Children are particularly vulnerable to errors. In 2012, French poison control centres published a study that identified, over a 2-month period, 169 reports of administration errors involving single-dose containers: 79% of the victims were children under 5 years of age. In 151 cases, the confusion was linked to the packaging. Two children suffered serious adverse effects (*Rev Prescrire* n° 345).

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

The recommended dosage for Flixovate° (*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 hypertension (*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 package 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 administration or provide information useful for patient care: the drug's name (INN), information on dosing, drug interactions, adverse effects, preparation and administration, 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 introduced: name change, different dosing device, usage broadened to include vulnerable 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 dangerous or unsuitable? And is the information about pregnancy ambiguous or has information about adverse effects been omitted?

Prescrire analyses the packaging of about 150 drugs every year, and has examined over 5000 products in the past 30 years.

Systematic analysis. Every item of the packaging is examined in detail using a standardised form. When the drug is part of an umbrella range, we compare its appearance with the other products in the range. We check the labelling for the legibility and position of key information (INN, dose strength, storage, etc.).

We test the quality of blister pack films and bottle caps, especially for dangerous drugs.

We test whether tablets are easily divisible. We prepare formulations that require reconstitution. We try out dosing devices, referring to the patient leaflet. We check whether oral delivery syringes could be attached to an injection needle. We taste and smell the drug. We analyse the usability and safety of the information provided, especially in the patient leaflet, including symbols, pictograms and dosing schedules.

1- Prescrire Editorial Staff "Drug packaging. A key factor to be taken into account when choosing a treatment" *Prescrire Int* 2011; **20** (120): 247-249.

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 Pegasys° (*peginterferon alfa-2a*) ready-to-use pen with a needle shield that conceals and protects the needle; and the Avonex°Pen° (*interferon beta-1a*) pen as an alternative to prefilled syringes.

There were improvements in the packaging of some drugs, but they were not sufficient to prevent all of the identified 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°, marketed for the treatment of cramps, is now packaged in blister packs instead of bulk bottles. This improvement does not justify 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 ▶▶

a- 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 unattached corner of film which can then be lifted in order to peel off the safety film.

b- 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 consultation 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 excipients (ref 2).