Translated from *Rev Prescrire* June 2012; 32 (344): 458-459

Packaging of medicines for paediatric use: Prescrire's constructive proposals

Abstract

● In May 2011, the European Medicines Agency (EMA) released for public consultation a draft guideline on the pharmaceutical development of medicines for paediatric use. *Prescrire* made 20 constructive proposals. Background information can be found at english.prescrire.org.

Rev Prescrire 2012; 32 (344): 458-459.

Children are at particular risk from the dangers created by the use of medicines. *Prescrire*'s 2011 overview of packaging highlights the need for a strong, clear guideline on the pharmaceutical aspects of the development of medicines, focusing first and foremost on the interests of children. Firstly the guideline needs to address medicines for paediatric use. Secondly, it should make current and future medicines safer, particularly those initially developed for adults and not approved for paediatric use but that we can assume will be administered to children because they fulfil a need that is unmet by the medicines currently authorised for children. The EMA/CHMP/QWP/180157 draft guideline offers opportunities for progress but its packaging component is grossly inadequate. Health authorities also urgently need to acquire more expertise in excipients.

***Prescrire* has 20 constructive proposals to help improve the EMA/CHMP/QWP/180157 draft guideline, focusing first and foremost on patients' interest:**

1. Early paediatric investigation plans

Encourage pharmaceutical companies to submit their paediatric investigation plans (PIPs) as early as phase II of drug development, rather than just before applying for marketing authorisation. PIP submission in phase II increases the chances that paediatric medicines whose pharmaceutical forms (including excipients) and packaging have been properly evaluated will become available.

2. Improve surveillance of supplementary protection certificates

For medicines that are candidates for a 6-month extension of their supplementary protection certificate under the European Paediatric Regulation, impose stricter obligations and closer supervision by European medicines agencies with respect to the safety, convenience and availability of paediatric medicines, and provide for financial penalties that shall apply when these obligations are not met.

3. Think about children when re-assessing medicines

For medicines that are no longer protected by a patent or supplementary protection certificate, encourage national medicines agencies to be much more vigilant and to set stricter requirements for the pharmaceutical aspects of medicines (dosage form, dose strength, package leaflet, excipients) in European worksharing procedures to re-assess medicines in children (Article 45 of the Paediatric Regulation) and in European referral procedures, particularly for the harmonisation of marketing authorisations (Article 30 of Directive 2001/83/EC).

4. Assessment of packaging by all medicines agencies

In medicines agencies and national pharmacovigilance organisations, raise the quality of and safety requirements for packaging to at least the level of the recommendations issued by the Council of Europe in 2006; increase their teams' resources and expertise in packaging analysis; create working groups to assess risks specific to packaging and to develop new solutions for safer, more convenient packaging; make children's safety a priority.

5. Improve public information on packaging

Improve the information provided by health authorities for healthcare professionals and patients: provide descriptions of packaging items and instructions for their use in the summaries of product characteristics (SPC) and package leaflets; when changes to packaging items are liable to affect the way they are used, develop teaching and training programmes; when a packaging item has caused errors or the potential for error clearly exists, publish a publicly accessible, detailed analysis, linked to or included in the public assessment report (EPAR, national, decentralised or mutual recognition procedure PAR) on the websites of the appropriate medicines agencies; when a new marketing authorisation or major variation is granted, publish publicly accessible mockups of all of the packaging items.

6. Unambiguous labelling of dose strengths and concentrations

With regard to labelling, amend European guideline EMA/707229/2009 on the expression of names, dose strengths and concentrations, focusing on the prevention of medication errors (20,21).

7. Clearly legible INN on labelling and packaging leaflets

Demand that drug regulatory agencies, pharmacoeconomic assessment agencies and pharmaceutical companies prominently display the drug's international nonproprietary name (INN) and dose strength on labelling and package leaflets, to ensure that medicines are identified by their true name, the INN. The European Commission should also promote the teaching of INNs to healthcare professionals from undergraduate training onwards, and encourage patients to learn them too. ▶▶

8. Readability and comprehension tests

Conduct readability and comprehension tests on patients and even healthcare professionals, addressing all of the information that is written or depicted graphically on packaging (package leaflets, labelling, pictograms, dosing schedules, etc.). Do not allow any graphical information onto packaging until it has been evaluated or if it was deemed unsatisfactory in tests.

9. Debate on the use of colours for a same range

Conduct a thorough debate in the European Union on the use of colours on packaging, particularly as a means to differentiate between various dose strengths from the same range, especially those intended for children.

10 to 15. Improving dosing devices

Dosing devices:
– ban multi-dose oral liquid forms that are not supplied with a dosing device, and educate users in the European Union on the dangers of measuring medicines with household spoons;
– evaluate solutions to ensure that patients can identify the correct dosing device for their medicine (label the device, fit bottles with plastic holders into which users can insert the dosing device) and strongly advise pharmaceutical companies to develop effective solutions;
– encourage the European Pharmacopoeia, European medicines agencies and the US Food And Drug Administration to collaborate in evaluating the safety and convenience of the various types of dosing device available, starting with the commonest ones: plastic spoons, cups, oral delivery syringes and droppers;
– demand that the harm-benefit balance of any new type of dosing device be evaluated and considered satisfactory before it can be introduced on the European market;
– determine what the best dosing device would be, such as an oral delivery syringe graduated in milligrams or units, and the most suitable capacity and accuracy, then take steps to ensure that it becomes the norm;
– promote user testing of dosing devices by target patient groups, checking that the instructions in the package leaflet are compatible with the dosing device; use the results to assess their quality and safety.

16. Child-proof cap

Demand that all bottles of oral liquid medicines be fitted with a child-proof cap.

17. Blister strips and unit doses

Demand that all tablets or capsules be packaged in blister strips, with individual labelling of each unit dose and a safety film for substances that are more dangerous than most drugs; ban bulk bottles, beginning with those that contain orodispersible drugs with enticing flavours (a French example being orodispersible *paracetamol* – Efferalganodis°) and substances that are fatal to children (e.g. *iron*, *methotrexate* and *quinine*).

18. Make sachets and patches safer

Develop ways to make sachets that contain dangerous powders and transdermal patches safer.

19. Publication of data on overdoses

Publish detailed data on overdoses and accidental poisoning with drugs or excipients in SPCs and public assessment reports; make them publicly accessible on the websites of European Union medicines agencies.

20. Improve information about excipients

Better inform healthcare professionals about the adverse effects of excipients. Set up a working group within the European Medicines Agency (EMA) concerned specifically with excipients, similar to the Herbal Medicinal Products Committee (HMPC). It would be responsible for centralising adverse effect data on excipients and for evaluating them, drafting monographs for each excipient, issuing clear recommendations on their use, publishing public assessment reports on the EMA website, including summaries of adverse effect data for each age group, and compiling lists of excipients that are eligible or ineligible for use in each age group.

The safety of children must be a priority of the evaluation procedure, bearing in mind that many drugs that are not approved for paediatric use are nevertheless administered to children.