Via electronic transmission

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Prescrire's response to the public consultation on EMA/CHMP/QWP/180157/2011 "Draft - Guideline on Pharmaceutical Development of Medicines for Paediatric Use": a pragmatic overview and 20 constructive proposals

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Paris, 29 December 2011

Dear Sir or Madam,

In May 2011, the European Medicines Agency (EMA) released for public consultation a draft guideline on the pharmaceutical development of medicines for paediatric use (1). The *Prescrire* team's opinion on the draft is set out below.

Introduction

The pharmaceutical aspects of a medicine are important to its harm-benefit balance; they include its dosage form, excipients, dose strength or concentration, and packaging.

A strong, detailed Community guideline on the pharmaceutical aspects of medicines developed for children will be a key determinant of the quality of the treatments available for young patients in the European Union.

Such a guideline will reinforce the advances expected from implementation of the European Paediatric Regulation (2).

Measures to benefit children should focus first and foremost on their real needs. The priorities for the many healthy children in the European Union are antenatal care, postnatal follow-up and primary prevention: of serious infectious diseases (through vaccination), obesity, accidents in the home, etc. (3). Measures are also required to regulate and evaluate the many off-label uses of medicines that are useful to children but not authorised for paediatric use, and to ensure that the treatments available to children are accessible, convenient and safe.

Prescrire has been analysing drug packaging since the early 1980s: our team has systematically examined the packaging of over 5000 medicinal products, many of which concern children directly or indirectly. We have published a number of annual reports of these analyses: for the French versions, select "*Les Cahiers Prescrire*" from the "*Libre accès*" dropdown menu at www.prescrire.org, then select "*Le conditionnement des spécialités pharmaceutiques*"; for the English versions, search on the term “packaging” at http://english.prescrire.org/en/.

In part I of this document, *Prescrire* presents a pragmatic overview of the current quality of drug packaging insofar as it affects children. The points made are illustrated with concrete examples. Many other examples can be found in *Prescrire*’s annual reports of its drug packaging analyses (4-10).

In part II, we present our proposals to help improve draft guideline EMA/CHMP/QWP/180157, focusing first and foremost on the interests of patients.

Part I – Drug packaging and children: *Prescrire*'s overview of the situation as of 2011

Far too often, the packaging of paediatric medicines creates a risk of medication errors and far too many dangerous medicines for paediatric or adult use are too easily opened by children.

I-1 ● Paediatric drug packaging too often potentially dangerous

Medicines agencies were already authorising the inclusion of information about the paediatric use of medicines in summaries of product characteristics (SmPC) and package leaflets before the European Paediatric Regulation of December 2006. But the sections on dosage, pharmacodynamics and pharmacokinetics rarely provide enough practical information on paediatric use and do not do enough to prevent medication errors.

Pharmaceutical forms and package leaflets not tailored to paediatric use. A great many package leaflets state that the drug can be administered to children, yet pharmaceutical forms and dose strengths specifically suited to children have not been manufactured.

One example is the package leaflet that accompanies sachets of *sodium picosulfate* powder for oral solution – Picoprep°, which was authorised through a European mutual recognition procedure. This drug is used to cleanse the bowel before an investigational procedure. We examined its packaging, including its leaflet, in 2011. The package leaflet of 2011 stipulates that one-quarter or half of a sachet should be administered to children under 9 years (4). But this package leaflet gives no advice on how to accurately prepare a quarter or half dose. This medicine is unsuitable for children in two ways: no paediatric dose strengths exist and the package leaflet does not contain enough information on dose preparation. These two flaws expose children to a risk of dangerous overdoses or failed bowel investigations.

Another example identified by *Prescrire* in 2011: as a result of a European worksharing procedure in which member state medicines agencies assessed the paediatric data on *mesalazine*, it was authorised for use in children aged 6 years and older. Although the treatment will be a useful addition to paediatrics, the dosage forms and dose strengths available in France are unsuitable for the youngest children for whom it is authorised (11).

Dosing devices: from poor quality to the potentially dangerous. The dosing device of a liquid paediatric dosage form (oral or injectable) is a key determinant of the quality and particularly the accuracy of the doses prepared. But the vast majority of dosing devices examined by *Prescrire* over the last 30 years have been inaccurate and/or unsuitable and often cause preparation errors (4-10). In 2009, the US Food and Drug Administration (FDA) came to a similar conclusion in its analysis of the packaging of 200 over-the-counter (OTC) drugs for children (12,13).

In the paediatric self-medication sector, the quality of dosing devices is too often substandard, even for drugs that contain dangerous substances. For example, various antitussives contain substances such as opioids (*dextromethorphan*, *pholcodine*) or phenothiazines (*oxomemazine, promethazine*). Despite the presence of these dangerous substances, the pack usually contains: no dosing device at all, forcing patients to use household spoons, a practice that should be prohibited since the capacity varies from one spoon to another (14); or commonly a measuring cup, yet in practice this is the dosing device associated with the highest risk of overdose (12,13); or an inaccurate plastic spoon.

The variety of dosing devices is limited: often pharmaceutical companies use the same model of mass-produced spoon, cup or oral delivery syringe graduated in millilitres for different medicines. This is the cheapest solution for them, so increases their profit margin. But it is not the best solution from a quality perspective. The problem with dosing devices graduated in millilitres is that a calculation must be performed to convert the milligrams of the active substance prescribed into the equivalent number of millilitres of medicine to be measured then administered.

Confusion between milligrams and millilitres is potentially dangerous. A mix-up of this type occurred in 2006 with the 60 mg/mL oral solution of *oxcarbazepine* – Trileptal°, resulting in an increased risk of adverse effects, particularly neurological and cardiac effects (15). In 2010, the pharmaceutical company UCB gradually replaced the syringe for Keppra° (100 mg/mL oral solution) for adults, which was graduated in milligrams of *levetiracetam*, with three oral delivery syringes, all graduated in millilitres, two of which were intended for young children (16). If the number of milligrams prescribed is confused with the number of millilitres, a 100-fold dose of the antiepileptic *levetiracetam* would be administered.

Syringes graduated in kilograms of the child's body weight are commonly used in France for paediatric medicines. The problem with this design is that the dose can only be adjusted to the child's weight. The total daily dose can be adjusted by varying the number of doses administered per day. Where different indications are treated with different doses, some SmPCs get round this problem by instructing the user to measure a quantity that does not correspond to the child's actual weight. For example, the French package leaflets for *domperidone* oral suspension state that doses of 0.25 mg/kg or 0.50 mg/kg of the child's body weight should be prepared, depending on the indication. To obtain a dose of 0.50 mg/kg, they instruct users to administer double the dose indicated for the child's weight (17). In France, a similar recommendation encouraging users to tinker with the child's weight to obtain the correct dose of *mequitazine* – Primalan° resulted in preparation errors, and the dosing device was consequently changed (18).

The capacity of some dosing devices is significantly greater than the dose to be administered: the most striking case in France was the *BCG vaccine* SSI°, whose syringe can contain 10 or 20 times more vaccine than the dose to be administered, depending on the patient's age (19). Overdoses were injected, resulting in severe local reactions, including abscess, lymphadenopathy and/or secondary infections. The number of overdoses reported decreased markedly in 2005 after health professionals were informed of the risk, but 36 cases were reported in 2007.

In all of these cases, the documentation released by the medicines agencies concerned includes no assessment of the risks associated with the dosing devices, yet accurate measurement of the dose to be administered is essential. Such an assessment should be performed for every pharmaceutical form, whether intended for children or adults, to determine the features that should be present in the safest dosing devices.

Labelling too often ambiguous or misleading. The labelling of medicines for children contains a lot of useful, critical information, beginning with the way the concentration of liquid dosage forms is expressed, which is a potential source of error.

In 2009, *Prescrire* and the International Medication Safety Network (IMSN) proposed alternatives to the dangerous recommendations in EMA/707229/2009 on the expression of dose strength and concentration in drug labelling (20,21). But these proposals were ignored. Yet children are the patients most at risk when dose strength is expressed in a way that fulfils its administrative purpose perfectly well but leaves the way open to medication errors.

In 2007, the way the concentration of *lopinavir* + *ritonavir* – Kaletra° oral solution was expressed probably contributed to the death of a baby (22).

Children are also among the patients most vulnerable to dangerous labelling on injectable drugs. In 2004, a child died in France when the wrong dose strength of an ampoule of *morphine* was selected. Following this tragedy, the French medicines agency (Afssaps) embarked on a major project to standardise the labelling of particularly dangerous injectable substances (23).

In addition, a European guideline on drug labelling advocating the prominent display of the international nonproprietary name (INN) has been in force since 12 June 2009 (24). Although this guideline contains positive recommendations, useful to the prevention of medication errors, it has hardly been applied and consequently has had almost no impact on the packaging examined by *Prescrire* in 2009, 2010 and 2011 (4,7,8).

Inappropriate pictograms and dosing schedule graphics. The outer packs of paediatric medicines tend to be plastered with pictograms, illustrations and dosing schedules.

In 2003, the Afssaps discovered that the outer pack of the psychotropic *niaprazine* – Nopron°, a phenothiazine authorised for insomnia in young children, had inappropriately attractive graphics for such a dangerous substance: a bird, a midnight blue background and a starry sky (25). The graphics were amended. But similar labelling was authorised in France in 2011 for a medicine containing *oxomemazine* (4).

In 2005, the outer packs of a medicine containing *alprazolam* displayed a pictogram showing a child (26). A statement in the "precautions for use" section had opened the way for its use in children, prompting the pharmaceutical company to add this pictogram, yet in twenty years, no data on the harm-benefit balance of *alprazolam* in children had been added to the clinical evaluation dossier.

In 2006, we discovered pictograms showing children with a beach ball on medicines containing either *citalopram* or *zolpidem*, yet the SmPC only authorised their use in adolescents from 15 years (the age considered by the French authorities as the threshold between adulthood and childhood) (27).

As of 2011, too many dosing schedule graphics (in which the dosing frequency is indicated graphically by boxes labelled morning, midday and evening, along with other information) contradict the authorised posology. To cite just one French example: *fluticasone* (cream, ointment) – Flixovate°, a highly potent topical corticosteroid, was authorised for the treatment of atopic dermatitis in infants aged between 3 months and 1 year. The SmPC stipulates it may only be applied once a day in this age group, while older patients can use 1 or 2 daily applications (28). The outer packs continue to show a dosing schedule consisting of two boxes labelled "morning" and "evening", which could cause confusion and dangerous overdoses (29). A statement next to the dosing schedule refers the user to the package leaflet, where the "*frequency of administration*" section states only: "*use as prescribed by your doctor*"! [*our translation*].

In all of these cases, far from providing information to aid the safe and effective use of the treatment, the graphics were misleading. Pharmaceutical companies can even turn a negative statement in the SmPC into graphics that encourage the use of the medicine. Who evaluates these graphics to ensure that they correctly convey the information intended? Why are they not systematically assessed by medicines agencies?

Umbrella brands: medicines are not toys or sweets. Whether intended for use by adults or children, most of the packaging shortcomings that can cause dosing errors are to be found in umbrella brands: look-alike labelling, fanciful graphics; poor quality dosing devices; bottles without a child-proof cap, etc. (4-10). Umbrella brands tend to trivialise medical treatment, yet often contain substances that are dangerous to young children if given in excessive doses.

The trend is slowly intensifying. For example, in 2011, *Prescrire* examined a syrup in the Humex° umbrella brand that contains the phenothiazine *oxomemazine*. The bottle does not have a child-proof cap. The pack contains a measuring cup, but in practice this type of dosing device often leads to overdosing (12,13). The outer pack and bottle show a pouring liquid that looks like a creamy caramel dessert. The term "night-time" is prominently displayed next to a moon with a midnight blue background and a starry sky (4). Users might assume that it is a treatment for insomnia, yet that is not its approved indication.

Babies: beware the spread of single-dose containers. Some containers are widely used for very different substances. Single-dose plastic ampoules are common in paediatrics. They may contain solutions for cleaning or disinfecting the eyes, ears or wounds, or for treating nappy rash, etc., exposing infants to the risk that the wrong product or route of administration will be used.

Some of these potential errors are worrying. For example, instilling *chlorhexidine* into the nose instead of *physiological saline* causes serious adverse effects (4-10).

Any policy to prevent medication risks must also take into account the other products that will be used concomitantly in certain situations, especially in paediatrics.

Learning from errors: a resource untapped by medicines agencies. In 2006, the oral delivery device for Rotarix° *rotavirus vaccine* was a syringe. It had no Luer hub, so could not be connected to a needle, but otherwise it looked very similar to a syringe for administering injections. The vast majority of vaccines are injected, and in several cases this oral vaccine was injected, using a different syringe from the one supplied in the pack (30). The packaging has since been improved, but patients are still not adequately protected. In some countries, an unusual oral delivery device was provided, in the form of a tube. This device also caused errors.

In the case of Rotarix°, the EMA has not released a thorough analysis of the errors that occurred with the oral delivery syringe or the tube (31). Similarly, there is no detailed official explanation of the causes of the fatal error that occurred with the oral solution form of *lopinavir* + *ritonavir* – Kaletra° (22). Another French example: serious adverse effects have been reported since 2006 after the administration of the paediatric drugs Uvestérol D° (*vitamin D*) and Uvestérol° A,D,E,C (*vitamins A, D, E and C*) to babies (malaises and serious episodes resembling choking, loss of consciousness, etc.), yet no detailed analysis of these events has been issued by the Afssaps (32).

1st packaging on the French market as a result of the Paediatric Regulation: disappointing and worrying. *Losartan* – Cozaar° was authorised for children with hypertension in 2009 in France. The Afssaps was notified 17 months later that the paediatric oral suspension would be marketed (4). As of late 2011, this form is difficult to obtain through the community pharmacy system in France and is not reimbursed by the French national health insurance system.

Many difficulties and errors are foreseeable as a result of the packaging used for the oral liquid form of *losartan* for children:

- the suspension is not ready to use, and the materials provided for its reconstitution and administration are conducive to error;

- the oral delivery syringe provided is graduated in millilitres, whereas the dose is prescribed in milligrams and calculations to convert the weight prescribed into the equivalent volume to measure are a potential source of error;
- the pack contains 473 mL of solvent whereas only 200 mL is required;
- the capacity of the bottle provided for the reconstituted suspension is 40 mL greater than required. There is therefore a risk of adding too much solvent and the drug being too dilute;
- this bottle is not labelled "*shake before use"*, yet shaking is essential to produce a uniform suspension.

Despite these serious flaws, *losartan*'s market monopoly has been extended by 6 months in France for all of its therapeutic indications in both children and adults, under the European Paediatric Regulation (2).

I-2 ● Too many dangerous drug substances are easily accessed by children

The ISO international standard on child-resistant packaging, the first edition of which dates from 1989, mentions in its introduction that: *"a significant number of suspected cases of ingestion by children of products used about the home is reported to the medical profession each year* (...) *and those that are associated with more serious side effects involve* (…)*, e.g. certain medicinal products, liquid fuels and solvents, strongly acid or alkaline preparations, and some garden products"* (33).

Blister packs have been used for a long time for dry dosage forms (tablets and capsules) in order to minimise this risk. Safety films that are more difficult to rupture or peel off than normal blister films make it harder still for children to remove and swallow tablets or capsules (34).

Yet too many tablets and capsules are still packaged in bulk bottles, making it very easy to take an overdose deliberately and accidentally. With very dangerous substances, even one tablet that falls unnoticed from the bottle and is found and swallowed by a young child would have serious consequences (4-10).

Sachets containing powder or transdermal patches are usually easy to tear open. Yet they are sometimes chosen by pharmaceutical companies and authorised by medicines agencies as the immediate packaging for very dangerous medicinal products, such as *nicotine* and *fentanyl* transdermal patches (35).

As of 2011, many drugs for oral administration (capsules, tablets, syrups, oral solutions, mouthwashes) are marketed in bottles without a child-proof cap, sometimes at doses that would be fatal to a child. Here are a few examples identified by *Prescrire* in recent years (4-10):

- oral liquid preparations: *acebutolol*; *clonazepam*; *dextromethorphan*; *diazepam*; *ethosuximide*; *metoclopramide; oxomemazine*; *paracetamol*; *pentoxyverine*; *pholcodine*; *tiapride*; etc.;
- tablets or capsules: *valproic acid*; *bromazepam*; *iron*; *methotrexate; nicotine* lozenges; orodispersible *paracetamol*; *paroxetine*; *prednisolone; quinine*; *tramadol*; etc.;
- mouthwashes with an alcohol content of 42.8%: *chlorhexidine* + *chlorobutanol*; etc.

For some of these products, such as *methotrexate*, *iron* and *quinine*, the dose accessible is fatal to children.

Child-proof caps have been around for a long time. They are inexpensive.

Yet bottles with caps that are easily opened by children continue to be authorised and left on the market by medicines agencies in the European Union. For dry dosage forms, blister packs with a safety film are still extremely rare: *Prescrire* sees only 4 or 5 a year in its packaging analyses (4-10). For liquid forms, child-proof caps are too rare.

I-3 ● Excipients: health authorities underestimate the risks

When adapting medicines to paediatric use, the dosage form must sometimes be changed, usually to an oral liquid form. The excipients must also be chosen judiciously, because they too have adverse effects, either through direct toxicity or by increasing the absorption and therefore the adverse effects of certain drugs.

Alcohol: what is the alternative for children? Alcohol is dangerous for children, but many oral liquid medicines contain a significant quantity of alcohol. These drugs too often have no child-proof cap.

For example, *Prescrire* examined two mouthwashes in 2011 containing *chlorhexidine* + *chlorobutanol* that had a high alcohol content (42.8%) and were coloured a shade of red that made them look like grenadine squash, a typical children's drink in France (4). The concentration of alcohol in medicines can be as high as 90% in France. A 2006 report requested by the Afssaps mentioned the dearth of paediatric data on chronic ethanol intoxication and the groups most at risk: it recommended that in principle paediatric medicines should never contain ethanol (36). Looking at the paediatric medicines on the market, it is clear that this recommendation is not being followed.

In 2011, the FDA blamed the excipients of the oral solution *lopinavir* + *ritonavir* – Kaletra° for serious adverse effects that occurred in preterm and full term newborn babies: the high alcohol content (42%) inhibits the metabolism of another excipient in this oral solution, propylene glycol, with the risk of it accumulating to levels that are toxic in this age group (4). This medicine is not recommended for children under the age of 2 years but is often used due to its antiretroviral efficacy. Yet the pharmaceutical company has not marketed any products in the European Union that are suitable for these young children.

Terpenic derivatives: often used as excipients. Various terpenic derivatives are used as active substances but just as often as excipients. Some of them induce neurological adverse effects in children. In 2011, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that their use in suppositories should be contraindicated in children under 30 months (37). But they are still present on the market in other paediatric forms.

Preservatives: dangerous particularly in off-label use. In 2001, the FDA issued a warning about the effects of intravenous administration of *benzyl alcohol*, which can cause

sudden onset of gasping respiration, hypotension, bradycardia and cardiovascular collapse; some deaths occurred (38). *Benzyl alcohol* is a preservative used in multi-dose injectable forms and its use is contraindicated in children. But when a paediatric dose strength is not available, multi-dose forms are sometimes administered to children, even if they are not approved for use in this age group.

Various other excipients, such as cremophor, parabens and *thiomersal* can cause bronchospasm (39).

The information about excipients in SmPCs and package leaflets is limited to qualitative lists. There are plans in 2012 to revise the concept paper on the information provided about excipients in labels and package leaflets (CHMP/463/00). Hopefully this will improve the current situation, by requiring the inclusion of information about their risks and by setting upper limits for their concentration.

In summary, children are not adequately protected from the adverse effects of excipients. Yet their risk of exposure to these effects is particularly high: through paediatric oral liquid forms; through off-label use of medicines developed for adults; through their increased susceptibility, which can be age-dependent for example; etc. The resulting dangers are all the more likely when packaging is substandard and dangerous.

Part II – A crucial need for a strong, clear guideline for children

Children are at particular risk from the dangers created by the use of medicines. *Prescrire*'s 2011 overview 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. 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 will become available whose pharmaceutical forms (including excipients) and packaging have been properly evaluated.

2. For medicines that are candidates for a 6-month extension of their supplementary protection certificate (SPC) 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. For medicines that are no longer protected by a patent or SPC, 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. 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 (40); 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 the information provided by health authorities for healthcare professionals and patients: provide descriptions of packaging items and instructions for their use in the SmPC and package leaflet; 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 mock-ups of all of the packaging items.

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

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

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

20. 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.

Conclusion

Our overview of paediatric packaging is worrying. Most is substandard or conducive to medication errors. Children are in too much danger.

Pharmaceutical companies have taken up the offer of financial incentives laid down in the European Union's Paediatric Regulation. Yet the quality of the paediatric packaging is often poor. In return for the lucrative 6-month extensions of their market monopoly that are granted to pharmaceutical companies, society has the right to expect effective regulation by the health authorities and paediatric medicines that are genuinely safe, easy to use and that reduce the risk of medication error. As of early 2012, that is not the case.

The EMA/CHMP/QWP/180157 draft guideline is a welcome advance but needs to do more to set pharmaceutical companies and member states' drug regulatory agencies on the right track. Significant improvements are required. The final guideline must be effective, and implemented as part of a dynamic process of continuous quality improvement that incorporates the lessons learned from analyses of medication errors, shared by European medicines agencies.

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