Rebuilding regulation after the Mediator° disaster: drug regulatory agencies must tackle the issue of packaging

The Mediator° disaster led to a major shake-up within the French drug regulatory agency in 2011 (see *Prescrire Int* n° 126 page 110). But the issue of packaging was overlooked in the raft of regulatory measures taken in 2011.

Packaging, the poor relation in drug re-assessments. For example, when commonly used paediatric drugs such as antitussives were re-assessed in France, their packaging was not questioned, although for the most part, it is dangerous (see inset page 135). Similarly, when *pholcodine* was reclassified as a prescription-only drug, no improvements in the packaging were imposed (see inset *Prescrire Int* n° 126 page 108).

The decision to improve the labelling of oral forms of *methotrexate* is a welcome move, but other aspects of the packaging of the drugs concerned remain unsafe. A better alternative to dangerous bulk bottles must be demanded, such as blister packs with a safety film and a device to help patients with limited dexterity remove tablets or capsules from the blister pockets.

As of 2011, *quinine* is unfortunately still marketed for cramps in France. Fewer patients will be exposed to its adverse effects now that it is no longer reimbursed by the French national health insurance system, but some patients will continue to be at risk (*Rev Prescrire* n° 337). The patient leaflets for the products concerned still do not inform patients about adverse effects, the bottle for Okimus° still has no child-proof cap, and blister packs containing Hexaquine° are still not labelled "*quinine*" (**a**).

The reclassification of *mequitazine* as a prescription-only drug does not alter the fact that the bottle is still not equipped with a child-proof cap and that a dose-measuring spoon is less accurate than a suitable oral delivery syringe (*Rev Prescrire* n° 337).

Restricting the prescription of *clonazepam* - Rivotril° does not alter the fact that the bottle has no child-proof cap, that a dropper is a less efficient dosing device than a suitable oral delivery syringe. In addition, the blister pack and patient leaflet for these tablets are difficult to read (*Rev Prescrire* n° 337).

Umbrella brands: evidence of the authorities' lax attitude towards packaging. The current state of the pharmaceutical market gives the impression that the French and European regulatory agencies are too often following the lead of drug companies on the issue of packaging quality, especially concerning 'umbrella" brands in the self-medication sector. In 2011, a ban on umbrella brands was still not forthcoming, and the problem continued to worsen with the authorisation of an *oxomemazine* product in a bottle with no child-proof cap, a dosing device (cup) liable to cause overdose, and unnecessarily fanciful labelling (*Rev Prescrire* n° 337).

Differences between originator drugs and generics: a matter for regulators. Differences in dose strengths, concentrations and product packaging between originator drugs and generic versions are a potential source of medication errors. For example, a change in the formulation of originator drugs containing *perindopril* led to a difference in the expression of dose strength from that of the generic versions, creating a risk of overdose (*Rev Prescrire* n° 316 and n,° 327). Risks are likely now that the dosage form and concentration of *docetaxel* - Taxotere° (*Rev Prescrire* n° 327) differ from generic versions. In 2011, a generic drug containing *lidocaine* + *adrenaline* was considered conducive to error because the concentration of *adrenaline* differed from that of the originator drug (1).

Drug regulatory agencies have a responsibility to focus first and foremost on patient safety in their decision-making and should anticipate practical differences between originator drugs and generics.

An initial reaction from the French agency in 2011. During the past year, *Prescrire* received a letter from the French agency responding to our 2010 packaging review (2). According to this letter, the agency is examining the cases presented in the review.

Furthermore, the French agency's project to re-assess marketing authorisations granted before 2005 will hopefully lead to the withdrawal of drugs with a negative harm-benefit balance, thus avoiding the need to modify their dangerous packaging. For drugs that are kept on the market, the project should place greater emphasis on packaging (3).

Analysing successes and failures. More generally, drug regulatory agencies should make a careful study of the pharmaceutical sector, specifically focusing on the issue of packaging, in order to identify successes as well as failures. They would then be able to guide pharmaceutical companies with full knowledge of the facts, so that they all develop safe, appropriate packaging, focusing first and foremost on the interests of the various types of patients who use their drugs.

a- The pharmaceutical company has announced that a blister pack labelled with INNs will soon be available.

Selected references from Prescrire's literature search

1- Afssaps "Différence de concentration en adrénaline entre la Lidocaïne Aguettant Adrénaline et Xylocaïne Adrénaline" avril 2011: 1 page.

2- Afssaps "Bilan 2010 du conditionnement paru dans Prescrire de février 2011" Courrier à *Prescrire* 8 août 2011: 2 pages + réponse de *Prescrire* 1 septembre 2011: 2 pages.

3- Prescrire "Permettre l'examen simplifié des modifications des termes des AMM purement nationales ? Oui, mais d'abord réévaluer les "vieilles AMM" nationales" Response to the public consultation of the European Commission 21 October 2011: 4 pages.

this drug is best avoided. Doses of *ethosuximide* - Zarontin° (*Rev Prescrire* n° 338) no longer have to be measured with an ordinary spoon, but the measuring cup that is now provided is a poor choice, since cups are known in practice to lead to overdose. As of late 2011, nasal *fentanyl* - Instanyl° was still marketed in dangerous multidose bottles with a dosing pump. Slightly less dangerous single-dose bottles became available at the end of 2011, but only in hospitals (*Prescrire Int* n° 123).

Droppers are still marketed: *diazepam* - Valium° (*Rev Prescrire* n° 338) and *clonazepam* - Rivotril° (*Rev Prescrire* n° 337). A welcome feature is a diagram on the opening tab of their outer packaging, showing that the dropper should be held vertically during use. Failing the provision of an accurate, suitable oral delivery syringe, it is high time that patient ►►