Translated from ***Rev Prescrire*** **February 2010; 30 (316): 143-145**

Drug packaging in 2009: a few advances

● **Once again, in 2009, most of the packaging that *Prescrire* analysed did not meet our quality criteria. Labelling information was too often ambiguous or clumsily expressed. The quality of dosing devices and the safety of multidose bottles were not guaranteed. Patient information leaflets were more legible on the whole, but once again rather uninformative. All of these shortcomings put patients at risk.**

● **European measures concerning drug labelling have finally been transposed into French law, and have led to some improvements: the international nonproprietary name (INN) is more frequently displayed on primary packaging. The use of Braille on boxes and access to Braille package leaflets are increasing. The improved legibility of the labelling of ampoules containing certain dangerous injectable drugs, as recommended by the French drug regulatory agency (Afssaps), has become more widespread.**

● **In practice, healthcare professionals need to take action on packaging issues: by choosing the best packaging, reporting potential sources of confusion and error and informing patients.**

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The *Prescrire* Packaging Working Group has noted that the packaging of drugs marketed in France has slowly improved over the last few years, although the general level of quality and safety remains unsatisfactory (1,2).

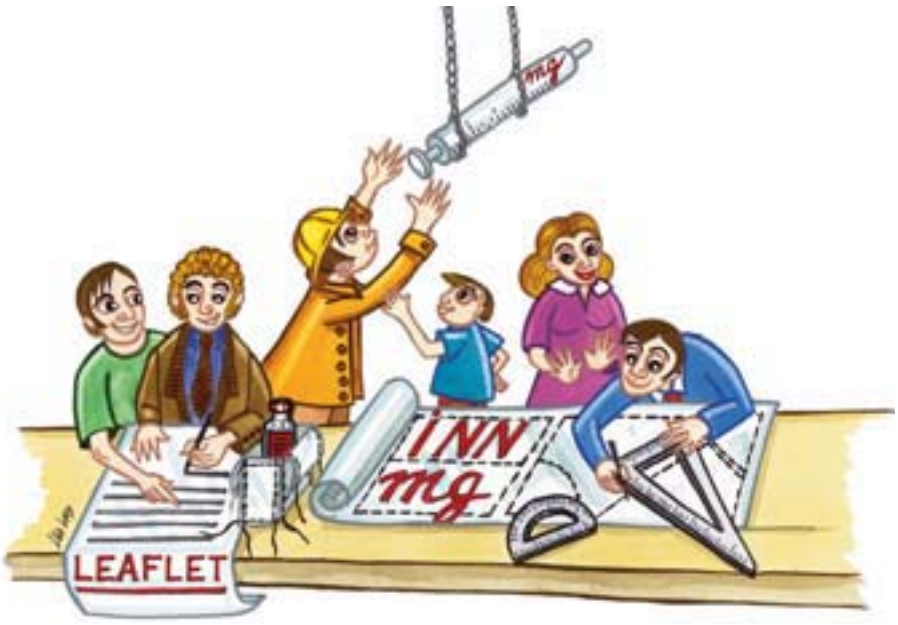
What was the verdict for 2009?

Most packaging did not meet our quality criteria

Overall, only slight progress was made in 2009.

INNs need to be more legible. Pharmaceutical companies that are not targeting the generics market often put the emphasis on invented brand names on the labelling, at the expense of the international nonproprietary name (INN).

For example, the INN is displayed under the brand name on blister packs in a virtually illegible form (small, widely spaced print), as though it is simply underlining the brand name (*racecadotril* - Tiorfast° *Rev Prescrire* 304 and 308, inside front cover). In another example, the INN was one-tenth the size of the brand name and compressed to fit under the first two letters of the latter (*nifuroxazide* - Imoseptyl° *Rev Prescrire* 307). The INN is mentioned after a variety of other particulars on the front of the box (*ziconotide* - Prialt° *Rev Prescrire* 312; *biclotymol* - Humex mal de gorge miel citron° *Rev Prescrire* 308; *chlorphenamine-paracetamol* - Humex état grippal° *Rev Prescrire* 314). As a final example, the INN disappears from the blister pack when the patient has to tear the film that covers the only identified blister in order to remove a tablet (*vildagliptin* - Galvus° *Rev Prescrire* 313).



Labelling cluttered with company graphics and multilingualism. Other factors make it harder to read the information that is useful for patient care, such as the INN and dose strengths: company graphics reproduced on the various product-line extensions (*telmisartan-hydrochlorothiazide* - Micardisplus°, Pritorplus° *Rev Prescrire* 306), particularly those of "umbrella" brands (*loperamide* - Imodiumcaps° *Rev Prescrire* 312; *pheniramine-paracetamol-vitamin C* - Fervex° *Rev Prescrire* 306); the use of shimmering colours (*guaifenesin* - Vicks Expectorant sirop adultes° *Rev Prescrire* 306), making it difficult to read the therapeutic indications, which are useful when selecting this over-the-counter drug, due to reflection from the metallic finish on some parts of the box.

The inclusion of multiple languages on blister packs or bottles leaves less size for the printed information, making it harder to read (*sitagliptin* + *metformin* - Janumet°, Velmetia° *Rev Prescrire* 304 and 314; *doripenem* - Doribax° *Rev Prescrire* 304) (**a**).

Lack of clarity in expression of dose strength and concentration. Too many labels in 2009 expressed dose strength or concentration in a complex way that was a dangerous source of confusion.

For example, a change in the expression of dose strength of *perindopril*, alone or in combination with *indapamide*, led to overdoses (Coversyl° *Rev Prescrire* 309, Bipreterax° and Preterax° *Rev Prescrire* 313). The total quantity of the active ingredient was still absent from the main parts of the labelling, such as the front of the box or the bottle label for some injectable drugs (*ziconotide* - Prialt° *Rev Prescrire* 312; *cetuximab* - Erbitux° *Rev Prescrire* 303; *triamcinolone* (*hexacetonide*) - Hexatrione° *Rev Prescrire* 308). ▶▶

a- In January 2009, the European Commission finally updated its guidelines on labelling and packaging leaflets (ref. 4). This new version includes useful recommendations such as displaying the INN in a prominent way. As of late 2009, it was still too soon to evaluate their impact. We will return to this issue in the future.

Drug packaging in 2009: a few advances

EMA withholding information: about packaging too

In 2009, a review of *Prescrire*'s requests for information addressed to the European Medicines Agency (EMA) between 2005 and 2008 revealed the agency's reluctance to provide clinical data (1).

In April 2009, *Prescrire* asked EMA for the labelling mock-up of the blister packs for *telbivudine* (Sebivo°), as the pharmaceutical company Novartis had been unwilling to provide it (2,3). On 5 June 2009, EMA refused to send us this mock-up, stating that the European right of access to administrative documents did not apply to this document, on the grounds of protection of commercial interests and intellectual property rights (2). *Prescrire* repeated its request on 9 June 2009, arguing that packaging mock-ups are technical documents held by EMA. They are just a two-dimensional representation of the authorised packaging. They show little industrial information, which could easily be concealed, if necessary. On 2 July 2009, EMA confirmed its refusal with no further explanation.

A drug regulatory agency is responsible for patient protection, not the commercial interests of pharmaceutical companies, and must guarantee free access to clinical data, including pharmacovigilance data and packaging mock-ups. Ideally, marketing authorisation (MA) decisions should include a complete representation of all packaging items.

1- Prescrire Editorial Staff "Legal obligations for transparency at the European Medicines Agency: Prescrire's assessment over four years" *Prescrire Int* 2009; **18** (103): 228- 233.
2- Prescrire Rédaction "Lettre à l'EMEA": 23 April 2009 + 9 June 2009: 2 pages au total + European Medicines Agency "Lettres à Prescrire" 5 June 2009 + 2 July 2009: 2 pages.
3- Novartis "Courriel à Prescrire" 29 May 2009: 4 pages.

► The risk of confusing concentration and total quantity is a concern with injectable drugs that require dilution or reconstitution. For example, in the case of *romiplostim* (Nplate° *Rev Prescrire* 311), the dose strength mentioned on the box and the bottle (250 µg) differ from the quantity contained in the bottle (375 µg) and from the target concentration for the reconstituted solution (500 µg/ml). Another example: although the box for Mycamine° (*Rev Prescrire* 305) does prominently display the total quantity of *micafungin* contained in each bottle of powder for reconstitution (50 mg or 100 mg), the target concentration for the reconstituted solution is only displayed in small print on one side of the box: 10 mg/ml or 20 mg/ml respectively. And this information is not present on the bottles (**b**).

Colours: still no guidelines. The use of colours, particularly to distinguish between various dose strengths within a product line, continues to expand. In 2009, several examples were analysed: *fentanyl* - Abstral° *Rev Prescrire* 313; *oxycodone* - Oxynorm°, OxyNormOro° *Rev Prescrire* 313; *lacosamide* - Vimpat° *Rev Prescrire* 307 + 311 inside front cover and 314; *levodopa + carbidopa-entacapone* - Stalevo° *Rev Prescrire* 309 and 314. Yet the risk-benefit balance of this practice has sometimes proved unfavourable (2). There is an urgent need for European directives aimed at improving these practices.

Inaccurate dosing devices. In 2009, psychotropic drugs were still supplied with inaccurate dosing devices: one antiepileptic (*diazepam* - Valium°, *Rev Prescrire* 306) comes with a dropper and another (*lacosamide* - Vimpat° *Rev Prescrire* 307 + 311 inside front cover and 314) comes with a measuring cup with barely legible graduations. And a simple measuring spoon was provided to prepare the dose of the cough suppressant *pentoxyverine* - Pectosan° (*Rev Prescrire* 306). Worse yet, the packaging of the antiepileptic drug *ethosuximide* - Zarontin° (*Rev Prescrire* 309) does not contain a dosing device - the package leaflet recommends using a household teaspoon, which is a known source of dosing errors.

Lack of safety devices. In 2009, multidose bottles containing large quantities of psychotropic drugs were still available on the French market without a childproof safety cap: *diazepam* - Valium° (*Rev Prescrire* 306), *ethosuximide* - Zarontin° (*Rev Prescrire* 309) and *pentoxyverine* - Pectosan° (*Rev Prescrire* 306).

In addition, the packaging for three drugs containing *perindopril*, alone or in combination with *indapamide*, was worse in 2009 than in previous years: blister packs were replaced by bulk bottles with no childproof safety cap. This makes it possible for a child to rapidly ingest an overdose, and imposes restrictions and repackaging costs on hospitals and healthcare institutions (*Rev Prescrire* 309 and 313).

Okimus° tablets (*dry hawthorn extract-quinine*, *Rev Prescrire* 309) have changed colour but the bulk bottle still has no childproof safety cap (for which it was given a red card in the 2008 *Prescrire* Packaging awards).

Two other cases represent a step backwards: injectable *aciclovir* - Zovirax° (*Rev Prescrire* 308) no longer comes with a drug transfer device and the syringe for the *papillomavirus vaccine types 6, 11, 16, 18* - Gardasil° (*Rev Prescrire* 306) is no longer equipped with an automatic needle guard. These devices were included in the packaging to reduce the risk of contamination through needle stick injuries.

Uninformative package leaflets. The patient information leaflets for self-medication products, including those available over the counter, often contain insufficient information. The natural course of the symptoms and non-drug options are only addressed briefly or not at all, for both cough (*guaifenesin* - Vicks Expectorant adultes° *Rev Prescrire* 306; *pentoxyverine* - Pectosan° *Rev Prescrire* 306) and fever (*pheniramine-paracetamol-vitamin C* - Fervex° *Rev Prescrire* 306). Another example: it is difficult to judge when a burn is serious enough to require medical attention on the basis of the package leaflet for *trolamine* - Biafineact° (*Rev Prescrire* 309), which recommends consulting a doctor for burns covering more than 2% of total body surface area.

Package leaflets start with a section describing the action of the drug. These sections have become more detailed, but they do not weigh the benefits against the adverse effects, which are only listed at the end of the leaflet. Some sections even contain promotional statements. For example, in 2009, the French package leaflet for *racecadotril* - Tiorfanor° (*Rev Prescrire* 307) mentions that the drug is "very effective", yet the reduction in the number of stools is modest at best.

In 2009, the *Prescrire* Packaging Working Group even analysed a drug that had no package leaflet per se: *betaine citrate* - Citrate de bétaïne Cristers° granules (*Rev Prescrire* 311). The information is spread around on the outer and inner surfaces of the box. The only information displayed on the sachet of granules is the batch number and expiry date. Once it has been removed from the box, this sachet becomes unidentifiable.

Furthermore, delays in updating package leaflets interfere with information about adverse effects reaching patients. For example, *Prescrire* obtained *aliskiren* - Rasilez° (*Rev Prescrire* 311) when it was introduced in May 2009. The package leaflet only mentioned two adverse effects: diarrhoea and skin rash. The risk of angioedema was not mentioned. This adverse effect was already known in 2007 and officially listed in the marketing authorisation dated 3 April 2009. Furthermore, when Rasilez° was introduced in France, a version of the package leaflet that mentioned this adverse effect was available on the European Commission's website.

High quality is possible

It is worth mentioning the progress resulting from the regulatory measures that required labelling to include the INN and Braille. These measures went into effect in France on 7 May 2009 (3). In 2009, with only a few exceptions, INNs were displayed, after the brand name, on the box and on the primary packaging (although rarely prominently). Braille was present on almost all of the boxes examined. And recalcitrant pharmaceutical companies no longer have the right to refuse access to Braille leaflets to associations for the visually impaired.

Improvements were made in the clarity of the labelling of ampoules containing certain dangerous injectable drugs, following Afssaps' recommendations (see opposite).

More blister packs that were examined in 2009 carried full labelling on each unit dose; most of these were for outpatient use. Blister packs with a safety film designed to delay access to the contents of the blisters were also less of a rarity: *dabigatran* - Pradaxa° *Rev Prescrire* 306; *oxycodone* - OxyNormOro° *Rev Prescrire* 313; *ambrisentan* - Voli-bris° *Rev Prescrire* 303; *fentanyl* - Abstral° *Rev Prescrire* 313.

Two oral syringes that used to be marked with two graduation scales (one corresponding to weight of drug and one in ml), which was a source of confusion, now only have graduations corresponding to weight of drug: *sodium oxybate* - Xyrem° *Rev Prescrire* 307 and *valproic acid* - Dépakine° syrup (*Rev Prescrire* 315). Another dosing device we examined in 2009, the oral syringe for Rovalcyte° oral solution (*valganciclovir*; *Rev Prescrire* 311) meets two criteria that are essential for quality care: it is graduated in mg and labelled with the INN.

Overall, the content of patient information leaflets has continued to improve, thanks to comprehension tests conducted on patients. Most of the high quality package leaflets were those authorised by the European Medicines Agency (EMA). Medical terms are explained. Certain information, such as the therapeutic indications, is presented in a concise manner. Examples of real progress include *bortezomib* - Velcade° *Rev Prescrire* 308, *doripenem* - Doribax° *Rev Prescrire* 304 and *lacosamide* - Vimpat° *Rev Prescrire* 307 + 311 inside front cover and 314 p. 899-900.

In practice. Improvement in drug packaging has been too slow. Healthcare professionals must therefore continue to remain vigilant, to report shortcomings and inform patients. Errors, suspected errors and dangerous packaging must be reported to Afssaps. Subscribers to *Prescrire* can also submit reports to its *"Preventing the Preventable"* programme for the prevention of treatment-related errors.

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b- In 2009, the European Medicines Agency (EMA) released draft guidelines for public consultation on the expression of concentrations and strengths on packaging. The comments Prescrire sent to EMA are presented in reference 5.

Labelling of injectable drugs: Afssaps makes progress

The French drug regulatory agency (Afssaps) began harmonising the labelling of ampoules of certain injectable drugs in 2005. Initially, 5 drugs were included: *adrenaline*, *atropine*, *ephedrine*, *potassium chloride* and *morphine* (1). In 2009, Afssaps added some other electrolytes, anaesthetics, *dopamine*, drugs used in dental practice, etc. (2).

INN and dose strength. In 2009, Afssaps published photographs of the ampoules before and after modification on its website (www.afssaps.fr) (2). Standardisation of information and its layout has made the labelling clearer. The main advances are that the international nonproprietary name (INN) is given greater prominence and the total quantity of drug present in the total volume of solution is displayed. Positioning the label along the length of the ampoule rather than perpendicular to this axis increases surface area for label information, making it more visible.

Reservations. Some information is still etched on the glass. It becomes difficult to read when layers of information are superimposed due to the transparency of the glass. Manufacturers need to explain why they cannot make more legible labels in their marketing application (1). But what could possibly justify the absence of a label on ampoules of Dopamine Aguettant°, Xylocaine° 50 mg/ 5 ml (*lidocaine*) and Naloxone Mylan° (2)?

More widespread application. These recommendations should be applied more extensively, beyond their official scope. For example, Mundipharma has applied them to the labelling of injectable *oxycodone* (Oxynorm°) 20 mg (*Rev Prescrire* 313). In 2009, the box showed the total quantity of *oxycodone* close to the total volume (20 mg - 2 ml) instead of just displaying the concentration "10 mg/ml" near the total volume, which is a potential source of errors. This type of improvement should be more widely applied.

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1- Prescrire Rédaction "Étiquetage des médicaments injectables: des progrès, à poursuivre" *Rev Prescrire* 2007; **27** (290): 903.
2- Afssaps "Référentiel comportant les photographies de l'ensemble des spécialités concernées par la 2e vague du plan d'harmonisation, avec un comparatif avant et après mise en œuvre des recommandations, classé par substance active et par laboratoire" October 2009: 92 pages.
3- Afssaps "Affiche générale" + "Affiche spécifique aux spécialités à usage dentaire" 10 décembre 2008: 4 pages.

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Drug packaging in 2008: not enough progress" *Prescrire Int* 2009; **18** (101): 134-135.
2- Prescrire Editorial Staff "Packaging of pharmaceuticals: still too many dangers but several encouraging initiatives" *Prescrire Int* 2007; **16** (89): 126.
3- Prescrire Editorial Staff " European Directive: drug packaging provisions finally transposed into French law" *Prescrire Int* 2009; **18** (102): 183-1.
4- European Commission "Guideline on the readability of the labelling and package leaflet of medicinal products for human use. Revision 1" 12 January 2009: 27 pages.
5- Prescrire Editorial Staff "Preventing errors related to the expression of strength on drug packaging" Comments on draft guidelines EMEA/208304/2009 28 May 2009: 9 pages.