▸ dose blister packs a benchmark packaging solution for quality care, but the technical means of child-proofing them have been available for some time (3).

In 2014, *Prescrire* granted a Packaging Award to the first tube we examined that had a child-proof cap: *brimonidine* cutaneous gel (Mirvaso°). Serious cases of ingestion by children had occurred during its clinical development. In 2015, another company placed *brimonidine* + *brinzolamide* eye drops on the market (Simbrinza°). The patient leaflet for these eye drops mentioned the risk of toxicity if a child were to ingest it, but the company and drug regulatory agencies did not go as far as adding a child-proof system (12).

Making packaging attractive to children increases the risk of accidental ingestion. For example, the *paracetamol* + *pheniramine* combination (Doli État grippal°) is a fruit-flavoured, pleasantly tart powder that tastes like candy. It contains doses of *paracetamol* that would be hepatotoxic for a young child. The box is easily opened and the sachets can be torn open by hand. Yet procedures exist to make boxes child-proof and manufacture sachets that can only be opened with a tool.

Regulators' low standards = a cause of poor-quality and dangerous packaging

Drug companies' marketing objectives or efforts to minimise manufacturing costs often undermine the quality of drug packaging. For packaging in the EU, pharmaceutical companies apply the regulatory requirements of title V, "Labelling and package leaflet", of the European Directive on medicinal products for human use (2001/83/EC) (2). These provisions are useful but too imprecise to ensure high-quality packaging. In practice, after examining the packaging of thousands of drugs, it is clear that pharmaceutical companies have considerable room to manoeuvre, which determines the quality or dangers of drug packaging. Bulk bottles or blister packs? Unit-dose or multidose immediate packaging? Accuracy and quality of the dosing device? A syringe graduated in milligrams of the drug or millilitres of solution? Should the brand name or the INN be most prominent? What level of childproofing is needed to prevent a child from ingesting a toxic quantity of the drug? The answers to all these questions are left above all to the pharmaceutical company.

Are agencies too flexible or do their priorities lie elsewhere? Drug regulatory agencies are generally not very demanding when it comes to the scientific quality of marketing authorisation applications. This is also true when it comes to packaging. Yet they have a role to play in ensuring that implementation of Directive 2001/83/EC meets the highest standards, by drawing up recommendations that protect patients (2).

When recommendations exist, agencies do not necessarily insist on their application. For example, the European Commission's 2009 guidelines on labelling recommend that INNs should be given equal prominence to brand names. These guidelines are very rarely applied, except for generic drugs. And the ANSM has still not published specifications for unit-dose presentations announced in 2008, or its recommendations on dosing devices launched in 2012.

Patient leaflet for Harvoni° (sofosbuvir + ledipasvir): almost no information on adverse effects

When we examined the packaging of Harvoni° (*ledipasvir* + *sofosbuvir*, a fixed-dose combination of two antiviral drugs with activity against hepatitis C), we were struck by the paucity of information about adverse effects in the patient leaflet. From the first version to the most recent one dated December 2015, the Harvoni° patient leaflet astonishingly mentions only two adverse effects: "*fatigue*" and "*headache*" (1).

Uncertainty over the adverse effects of sofosbuvir. *Sofosbuvir* monotherapy was approved in January 2014 under the brand name Sovaldi°. In our initial evaluation of this drug, we highlighted that the main clinical trial data available about adverse effects were difficult to interpret, due to inadequate evaluation (2). The European patient leaflet for Sovaldi° mentions the adverse effects of treatment with the combination of *sofosbuvir* and *ribavirin*, with or without *peginterferon*, but not for *sofosbuvir* alone (3).

However, animal data from rats and dogs that received high doses of *sofosbuvir* show potential haematological, hepatic, gastrointestinal and cardiac toxicity (1). The European Medicines Agency (EMA) is aware of these findings, but they are not mentioned in the European patient leaflet for Sovaldi° (2). The patient leaflet features the inverted black triangle symbol indicating, as for any new drug, that limited knowledge has been acquired on their adverse effects (2). But this warning sign is not generally expanded upon by additional information about the specific suspected harms that healthcare professionals and patients should look out for. Yet it is not a rare occurrence that drugs' suspected harms materialise and are subsequently mentioned in the adverse effects section.

In addition, the US prescribing information for Sovaldi° also encourages monitoring of *sofosbuvir*'s pancreatic toxicity due to the lipase elevation in certain patients (4).

Patient leaflet for sofosbuvir + ledipasvir: adverse effects that have gone unmentioned. This information has not been mentioned either in the patient leaflet for the *sofosbuvir* + *ledipasvir* fixed-dose combination, which simply warns of cases of fatigue and headache (1).

Yet the clinical evaluation data includes a randomised comparative trial ("Sirius") that provides evidence of several adverse effects of the *sofosbuvir* + *ledipasvir* combination (5). A variety of other disturbing adverse effects were reported in this trial: sleep disorders, pancreatic disorders, hypertension, cough and dyspnoea. Cases of elevation of creatine kinase activity raise the possibility of muscular harms. Preclinical data showed accumulation of *ledipasvir* in the uvea, with pigmented iris (5).

Patient leaflets must protect patients. Patient leaflets make a particularly important contribution to patient safety. The patient leaflet for the *sofosbuvir* + *ledipasvir* combination does not fulfil this function, and the EMA was too lax in its failure to demand that it contain information to protect patients and provide guidance about the kinds of adverse effects they should be looking out for. The Harvoni° patient leaflet, as it currently stands, should never have been authorised.

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Selected references from Prescrire's literature search.

1- European Commission "Chronological list of variations up to 7 January 2016 + patient leaflets from 17 November 2014 and 18 December 2015Harvoni": 15 pages.

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3- European Commission "Chronological list of variations up to 7 January 2016 + patient leaflets from 16 January 2014 and 27 May 2015-Sovaldi": 14 pages.

4- US FDA "Prescribing information-Sovaldi" 6 December 2013: 30 pages.

5- Prescrire Editorial Staff "Ledipasvir + sofosbuvir. A therapeutic advance in genotype 1 hepatitis C virus infection, despite uncertainties" *Prescrire Int* 2015; **24** (166): 285-289.

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