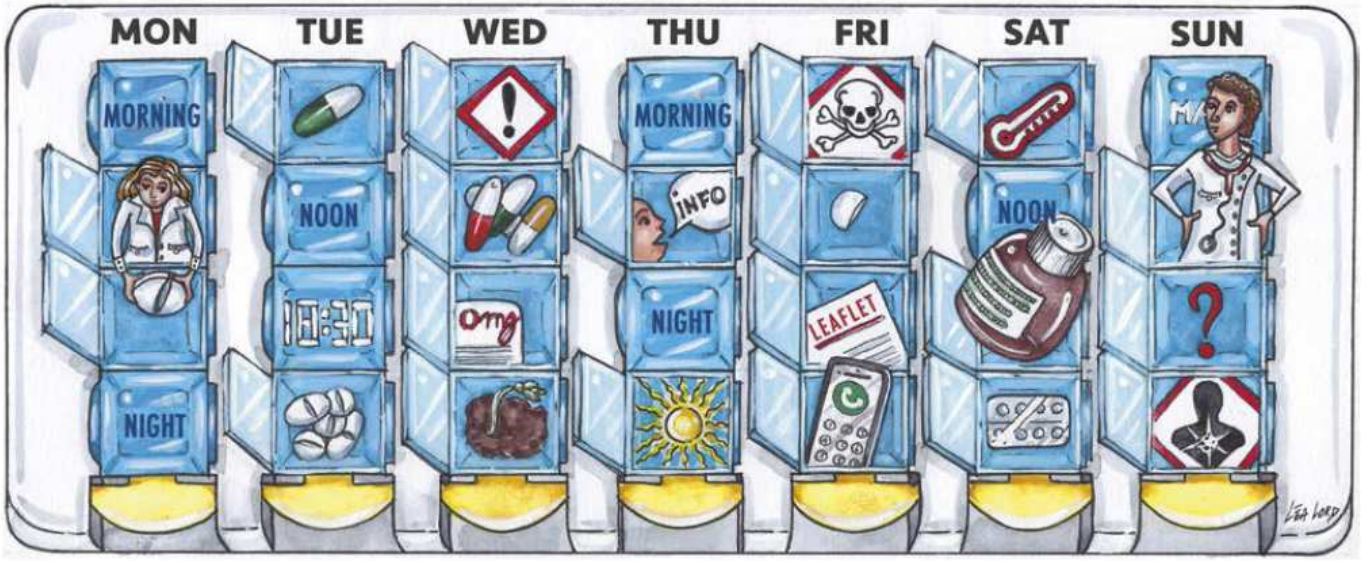
Prescrire's approach to labeling, packaging and naming related errors

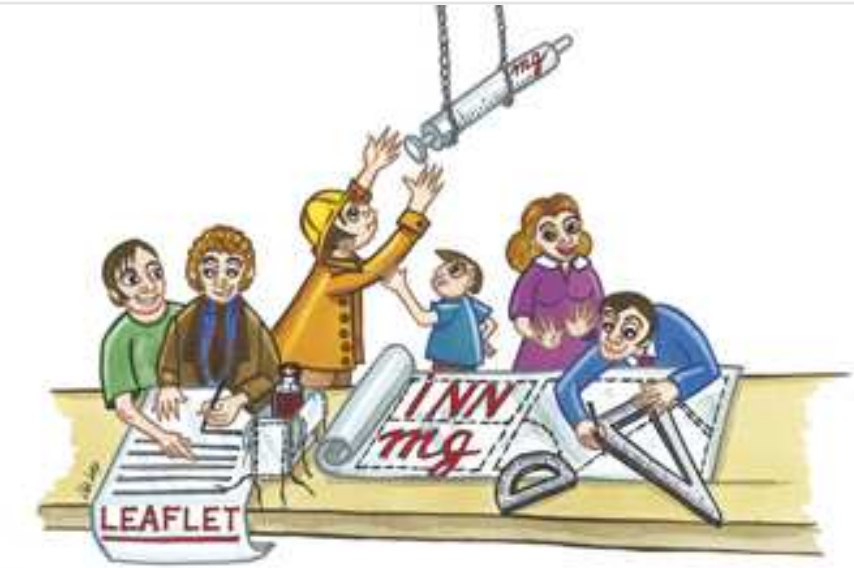


Dr Étienne Schmitt
Prescrire Editorial staff member
Head of *Prescrire* Programme Éviter l'Évitable (Preventing the Preventable)

Prescrire's analysis and risk assessment of packaging

- ***Prescrire*'s approach to choosing medicines**
- **Packaging-related errors reported by *Prescrire***
- ***Prescrire*'s analysis of packaging: know how** (quick reference)
- **Findings from *Prescrire*'s packaging analysis**

Prescrire's approach to choosing medicines



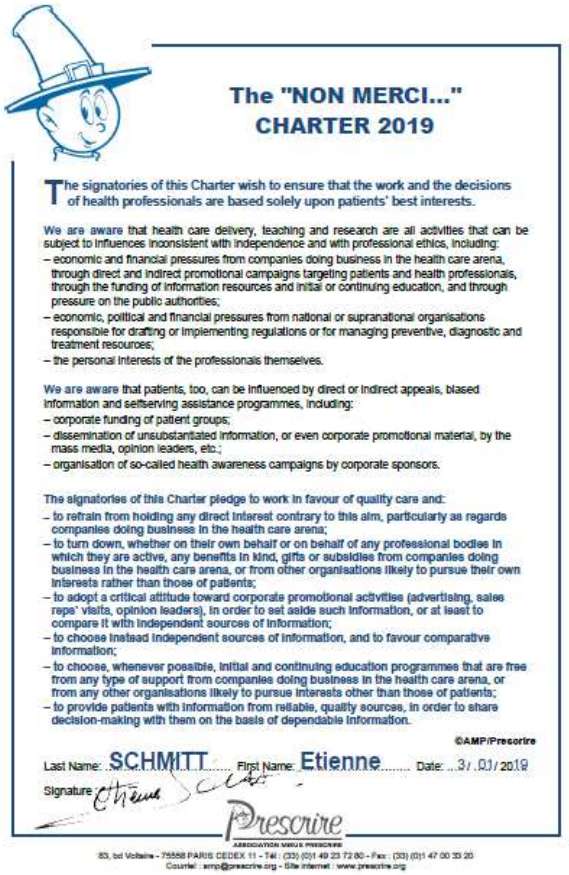
wisely
patient' interest first
independently

Prescrire Editorial Staff: no conflicts of interest

Prescrire's editors
are healthcare professionals
free from conflicts of interest

Prescrire's organisation
is structured so as to be
free of any influence from
pharmaceutical compagnies
or healthcare institutions

Prescrire's purpose is
« *to work, in all independence, in favour of quality healthcare, first and foremost in the interest of patients* »



The "NON MERCI..." CHARTER 2019

The signatories of this Charter wish to ensure that the work and the decisions of health professionals are based solely upon patients' best interests.

We are aware that health care delivery, teaching and research are all activities that can be subject to influences inconsistent with independence and with professional ethics, including:
- economic and financial pressures from companies doing business in the health care arena, through direct and indirect promotional campaigns targeting patients and health professionals, through the funding of information resources and initial or continuing education, and through pressure on the public authorities;
- economic, political and financial pressures from national or supranational organisations responsible for drafting or implementing regulations or for managing preventive, diagnostic and treatment resources;
- the personal interests of the professionals themselves.

We are aware that patients, too, can be influenced by direct or indirect appeals, biased information and selfserving assistance programmes, including:
- corporate funding of patient groups;
- dissemination of unsubstantiated information, or even corporate promotional material, by the mass media, opinion leaders, etc.;
- organisation of so-called health awareness campaigns by corporate sponsors.

The signatories of this Charter pledge to work in favour of quality care and:
- to refrain from holding any direct interest contrary to this aim, particularly as regards companies doing business in the health care arena;
- to turn down, whether on their own behalf or on behalf of any professional bodies in which they are active, any benefits in kind, gifts or subsidies from companies doing business in the health care arena, or from other organisations likely to pursue their own interests rather than those of patients;
- to adopt a critical attitude toward corporate promotional activities (advertising, sales reps' visits, opinion leaders), in order to set aside such information, or at least to compare it with independent sources of information;
- to choose instead independent sources of information, and to favour comparative information;
- to choose, whenever possible, initial and continuing education programmes that are free from any type of support from companies doing business in the health care arena, or from any other organisations likely to pursue interests other than those of patients;
- to provide patients with information from reliable, quality sources, in order to share decision-making with them on the basis of dependable information.

©AMP/Prescrire

Last Name: SCHMITT First Name: Etienne Date: 3 / 01 / 2019

Signature: Etienne Schmitt

Prescrire

83, bd Voltaire - 75568 PARIS CEDEX 11 - Tél : (33) (0)1 49 23 72 80 - Fax : (33) (0)1 47 00 33 20
Courriel : amp@prescrire.org - Site internet : www.prescrire.org

Prescrire's criteria for evaluating drugs

Prescrire evaluates new drugs' potential therapeutic advance, based on their harm-benefit balance

1. **Efficacy**
2. **Adverse Reactions**
3. **Convenience of use**

   an important component of a drug's harm-benefit balance

What are the functions of drug packaging?

- **The drug's box: 1st first source of information**

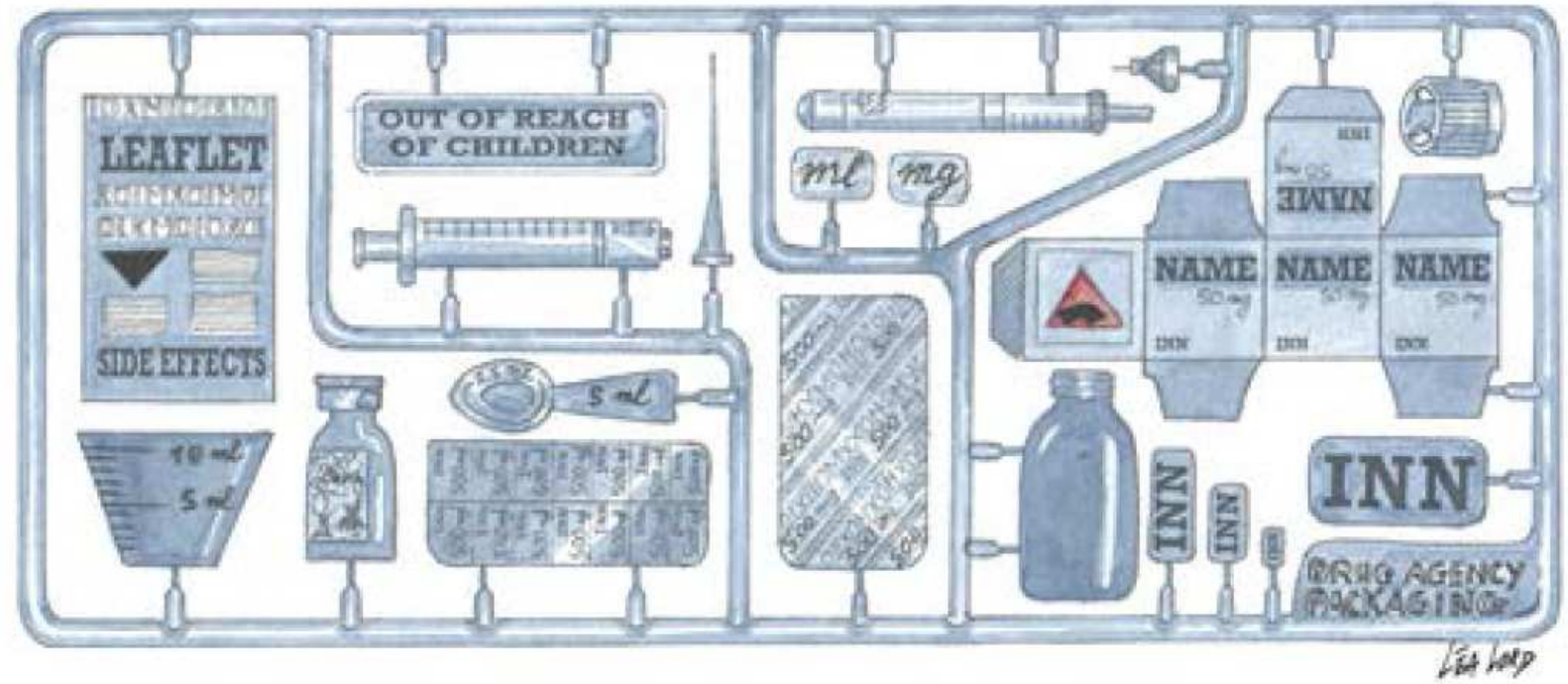
  active substances in the drug, using their international nonproprietary name (INN), their dose strength, and how it is administered and stored

- **Useful tools inside the box**
  - immediate packaging protect drug from knocks, light, temperature variations, contamination
  - safety devices: safety caps or childproof blisters
  - dosing device designed to prepare doses with appropriate accuracy
  - package leaflet help prevent preparation errors and to provide information about the drug's adverse effects, interactions and storage conditions.

What are the features of a safe packaging?

- The drug is ready to use
- Each dose is individually packaged and labelled
- The international nonproprietary name (INN) of each active ingredient is prominently displayed on the box and primary packaging (i.e. blister pack, bottle, sachet, etc.)
- Other information useful for preventing harm is clearly legible: dose strength, route of administration, storage conditions
- The dosing device is appropriate and accurate
- The drug can be easily distinguished from other drugs within the same product line
- The patient leaflet is clear, legible and informative, especially with regard to risks
- Child-proofing measures are taken to prevent accidental ingestion by children.

Packaging-related errors reported by Prescrire



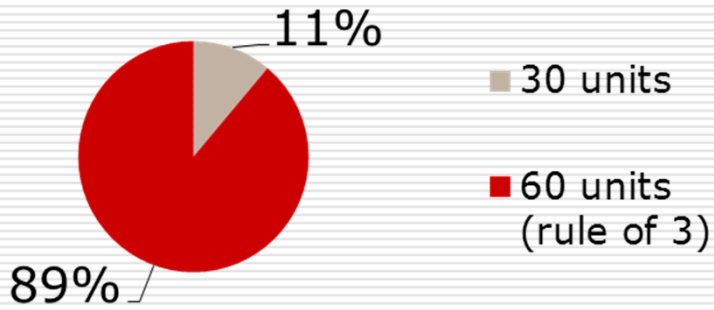
High-strength insulins unnecessary conversions

Humalog Kwikpen° 200 UI/ml

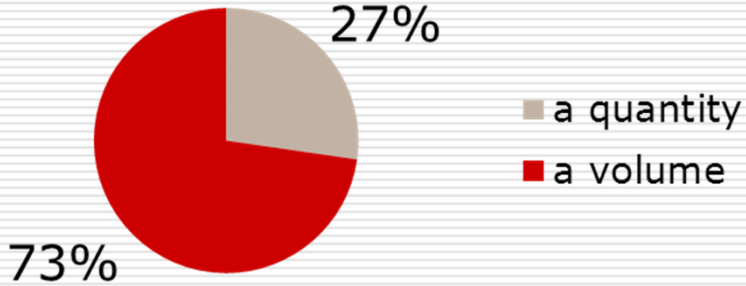
Humalog Kwikpen° 100 UI/ml

- In a hospital setting, a pharmacist offered a nurse insulin lispro Humalog Kwikpen 100 units / ml instead of Humalog Kwikpen 200 units / ml, not available in the hospital. She reacted to this replacement: "*but I will have to put 100 IU to have the 50 IU prescribed, since it is less concentrated*". Explanations within the healthcare team with pharmacists helped to prevent an error.
  A survey was then conducted in care units to assess how this risk of error was managed in current practice.
- In community pharmacy, 2 dispensing errors with serious consequences were reported to the French Health Products Agency (ANSM). Insulin lispro Humalog° 200 units/ml was dispensed instead of Humalog° 100 units/ml, and the patients were mistakenly advised to halve the doses, resulting in hyperglycaemia.

30 units from a 200 units/ml pen?
(100 units/ml pen only available)



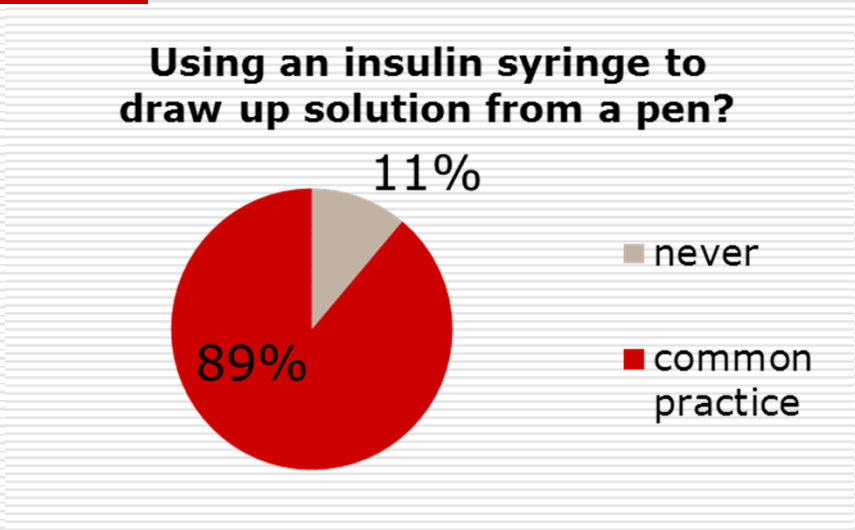
units, but what's?



Prescrire Rédaction "Insulines concentrées : penser et agir en unités d'insuline pour éviter les erreurs" *Rev Prescrire* 2018 ; **38** (420) : 752-754.

High-strength insulins withdrawn from pens with syringes

- A risk identified by the ISMP and the NHS, leading further to an EMA PRAC recommandation on May 2017
- Bypassing the dose counter is a misuse of insulin pens:
  - sometimes as a consequence of a calculation error
  - demonstrating that pens do not prevent their use as multidose vials
- The insulin syringes available in France are only suitable for insulin at a strength of 100 units/ml, the only strength available in multidose vials.
- The use of such syringes with high-strength insulins (200 units/ml or 300 units/ml) carries a risk of administering a double or triple dose.



Prescrire Rédaction "Insulines concentrées : penser et agir en unités d'insuline pour éviter les erreurs" *Rev Prescrire* 2018 ; **38** (420) : 752-754.

Deadly errors due to tramadol oral solutions

A 3-year-old child died of a tramadol overdose because a Doliprane° (paracetamol) pipette was used to prepare the dose. Other, sometimes fatal, tramadol overdoses have been reported in children, in particular due to confusion between the number of drops per dose and the number of drops per kg of the child's body weight.

Prescrire Editorial Staff "Tramadol: fatal overdoses in children" *Prescrire Int* 2017 ; **26** (179) : 44-45.

***roxine*) SERB (*Rev Prescrire* n° 389) • Contramal° Grünenthal and Topalgic° Sanofi Aventis, 100 mg/ml oral solutions (*tramadol*) (*Rev Prescrire* n° 397)**

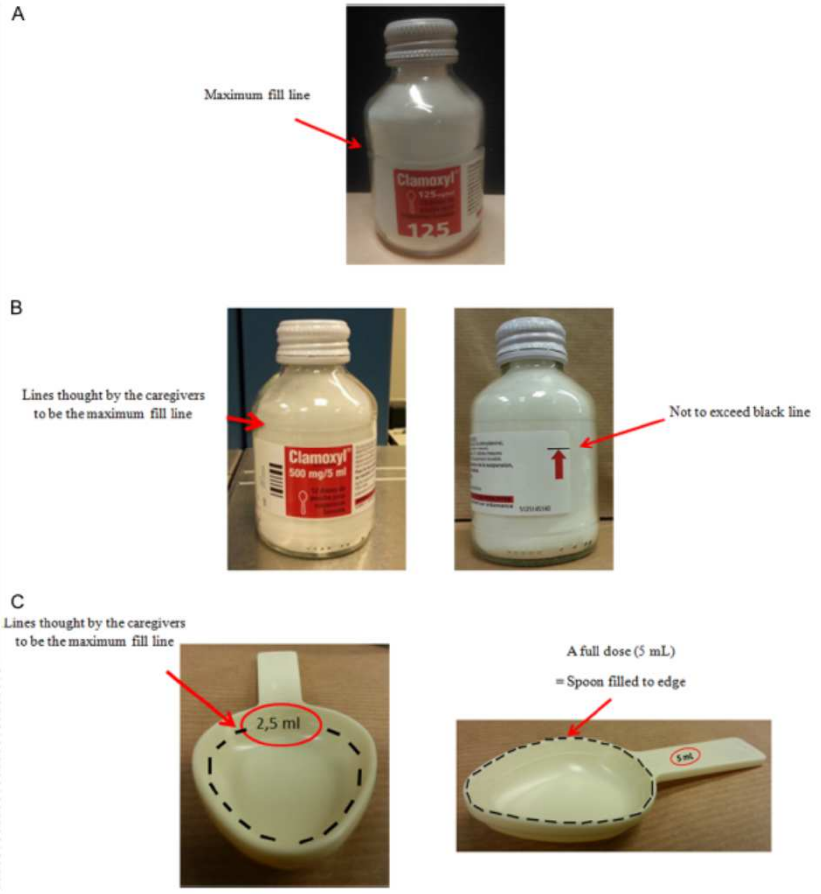
The dosing device supplied with the bottles of these drugs for dose preparation is a dropper, a device known to cause dosing errors, especially when a large number of drops must be counted. These solutions are highly concentrated, increasing the risk of an overdose or underdose if the drops are miscounted. Given that the adverse effects of *tramadol* are dose-dependent and *levothyroxine* has a narrow therapeutic index, it is particularly important to count the number of drops of these drugs accurately.

Paediatric oral liquid medication dosing errors by caregivers

Table 2 Reconstitution of bottles and dose preparation for Clamoxyl (amoxicillin) and Josacine (josamycin)

	Clamoxyl N=50	Josacine N=50
Reconstitution of the oral liquid medication		
Correct	27 (54%)	22 (44%)
Resulting in overdosing	3 (6%)	23 (46%)
Resulting in underdosing	16 (32%)	2 (4%)
Clumps*	4 (8%)	3 (6%)
Dose preparation		
Resuspending	10 (20%)	10 (20%)
Correct preparation	22 (44%)	45 (90%)
Overdosing identified	0 (0%)	0 (0%)
Underdosing identified	28 (56%)	5 (10%)

Results are shown as numbers and percentages.
*The presence of clumps may lead to either overdosing or underdosing.



Berthe-Aucejo A and coll. "Evaluation of frequency of paediatric oral liquid medication dosing errors by caregivers : amoxicillin and josamycin" *Arch Dis Child* 2016 ; **101** (4) : 359-364.
Presented in: Prescrire Rédaction "Formes buvables à reconstituer Clamoxyl° et Josacine° : erreurs fréquentes" *Rev Prescrire* 2016 ; **36** (396) : 746.

Colchicine: administration of a fatal overdose to a child

According to a case report with toxicological data published in France, a 4-year-old child weighing 16 kg was admitted to hospital for unexplained fever. Pericarditis was diagnosed and *colchicine* was prescribed at a dose of 0.5 mg per day for familial Mediterranean fever.

As a result of an unspecified "*failure in the monitoring of drug prescribing*", **"mg per day" was mistaken for "mg per kg per day"**, which is a common way of expressing doses in paediatric prescribing. The child received a dose of 0.5 "mg per kg per day" (8 mg per day) for two consecutive days, and thus a total of 16 mg of *colchicine*. The child died about 48 hours after the first dose of *colchicine*.

The article does not describe the circumstances surrounding the error, how the medication use system was organised, or why such a large quantity of *colchicine* was available on a paediatric ward .

Colchicine Opocalcium° tablets (***colchicine***), **Colchimax°** tablets (***colchicine + opium powder + tiemonium***) Mayoly-Spindler (Rev Prescrire n° 402, Prescrire Int n° 187)
For lacking any specific safety features to make it harder for children to gain access to the tablets, which could result in a potentially fatal *colchicine* overdose. The box could have a safety catch, or the blister pack could have a child-resistant film, combined if necessary with a tool to help remove tablets.

Prescrire Editorial Staff "Death of a child from a colchicine overdose" *Prescrire Int* 2017 ; **26** (187) : 166-167.

Learning from Healthcare Error Experiences

- Substitution between generics
- Fixed dose combinations
- Graduations of a dosing device
- Confused similar outer packages

Prescrire's assessment of packaging: know how

Prescrire's
Packaging Working Group

What are the drug packaging assessed by *Prescrire*?

- new drugs evaluated in the "New Products" section of its French edition, *La revue Prescrire*
- existing products when changes are introduced:
  - name change (is the INN harder to read?)
  - product size (is the closure too weak?)
  - different dosing device (is the device more accurate?),
  - usage broadened to include vulnerable patients: children, pregnant women (is the information about pregnancy ambiguous?), patients with renal impairment,
  - major new data on adverse effects (has information about adverse effects been omitted?)
  - broadening of ranges, in particular umbrella ranges, etc.
- around 7000 packages analysed in 38 years; 220 in 2018

Prescrire's Packaging Working Group

- Part of the "Information search - Companies and Agencies Unit"
- Knowledge resource on regulations on packaging and labelling
- Access to high level information on packaging and marketing authorisation files (upon request to the EMA and companies)
- Network with hospital pharmacists

- Every item of the packaging is examined in detail, i.e. the PWG
  - compare the appearance with the other products in the range, in particular if the drug is part of an umbrella range
  - check the labelling for the legibility and position of key information (INN, dose strength, storage, etc.)
  - test the quality of blister pack films and bottle caps, especially for dangerous drugs
  - test whether tablets are easily divisible
  - prepare formulations that require reconstitution
  - try out dosing devices, referring to the patient leaflet
  - check whether oral delivery syringes could be attached to an injection needle
  - taste and smell the drug
  - analyse the usability and safety of the information provided, especially in the patient leaflet, including symbols, pictograms and dosing schedules

A 2 steps approach

- 1st systematic assessment of packaging by the *Prescrire* Editors from the New Products section
- 2nd systematic assessment of packaging by *Prescrire's* Packaging Working Group
- Annual drug packaging review published in March *Prescrire* and in June *Prescrire International* issues

1st systematic assessment by the *Prescrire* Editors

- Quality or risk factor taken in account as soon as from the documentation stage: is the packaging a key factor?
- Planning of the stage of the New Products section editing process needing particular information on the packaging
- One of the key elements of the *Prescrire* article and of the editor analysis

Prescrire's criteria for assessing the packaging

Basic questions to be answered

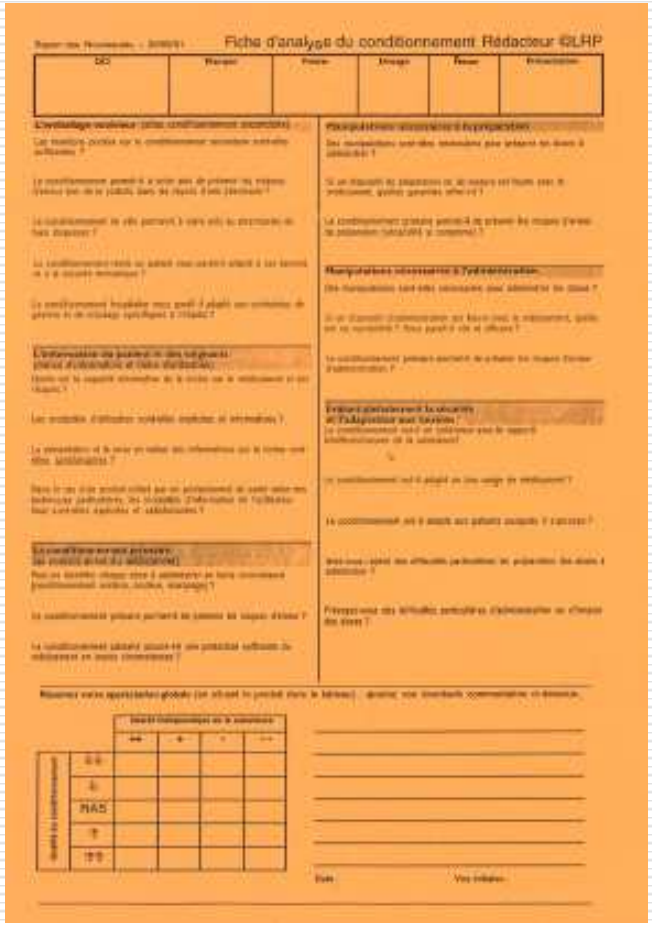
- Is it clear from the labelling which active substance or substances the product contains?
- How are doses prepared and administered?
- Does the information in the patient leaflet help users prepare doses correctly or are errors likely?

Factors taken in account

- situations in which the drug will be administered
- patients concerned, in particular vulnerable populations such as children, pregnant women and elderly patients
- setting in which it will be used (hospital or community) and supplied (on prescription only, over the counter at a pharmacy, or off the shelf)

Prescrire staff editor' packaging analysis worksheet

- Outer packaging
- Information needed by patients and healthcare givers
- Immediate packaging
- Operations related to the preparation of a dose
- Operations related to the administration
- Global assessment of the safety and convenience



Summary of the packaging global assessment

👍👍	**Packaging fully contributing to a safe and helpful use of the drug**	*Offers an advantage by preventing a particular risk or improving the quality of use (by the patient or by the healthcare giver) and/or of the drug use process*
👍	**Packaging potentially hepful for a correct use of the drug**	*Presents interesting characteristics, but still room for improvement in the interest of patients and et healthcare givers and/or better fitted to the drug use process*
NTR	**Usual packaging whithout particular interest**	*Does not distinguish, positively or negatively, by a particular quality or defect having any consequence on the drug use and/or the drug use process*
👎	**Packaging presenting defects jeopardizing the correct use of the drug**	*Globlaly few satisfying quality exposing to a risk of wrong use, or misuse and/or therapeutic inefficacy*
👎👎	**Packaging with important failures leading to serious risks during its use**	*Dangerous : very insufficient quality exposing to a risk of wrong use, or misuse including serious potential clinical consequences*

Quality of the packaging	Therapeutic interest of the substance			
	++	+	-	- -
👍👍				
👍				
NTR				
👎				
👎👎				

© Alain Savino/Prescrire

2nd systematic assessment by *Prescrire* Packaging Working Group

- After publishing each issue:
  - Centralized depository of the packaging elements used as documentation
  - Update of a table summarizing the packaging analysis
  - Overview of the corresponding packages
- Monthly meeting with the chief editor with special emphasysis on positive and negative findings, packaging editing themes, etc.
- Selection of candidates to packaging awards
- Orientation of the annual packaging review

Drug names reviews

- Systematic drug names reviews by the *Prescrire*'s Packaging Working Group
- Confusion between brand names: "Not to be confused" section
- Generic brand names masking the real name (INN): "Copies unmasked" section
- INN or common stems prone to error: "Common stem of the month" section

NE PAS CONFONDRE

Nous signalons ici certains produits de santé, qui
en
de
ou de condition

COPIES DÉMASQUÉES

Nous signalons dans cet encadré la composition des copies arrivées récemment sur le marché français sous un nouveau nom commercial de fantaisie, nom le plus souvent peu infor-

A drug's real name INN
INTERNATIONAL NONPROPRIETARY NAME

Translated from *Rev Prescrire* May 2015; 35 (380): 343

COMMON STEM -ciguat

Specific packaging reviews

- Comparative assessment of current available products in order to help the choice by healthcare practitionners and patients
- Focused on life threatening products
  - Oral iron salts packaging (2002, 2007, 2017, 2018)
  - Oral methotrexate
  - Colchicine, nicotine substitutes, etc.

- Focusing on practices and safety of use
  - Oral dosing devices
  - Vaccines

Subscribers letters or reports to Prescrire Programme Preventing the Preventable

- Feedback from subscriber reports
  - in a specific part of a learning column "Cogitations" entiled "Learning from Healthcare Error Experiences "
  - as narrative summaries completing an article, entitled "Seen from Preventing the Preventable"
  - as a reference backing an article on the reported problem
- Letters provide useful informations about error risks and sources of confusion, in particular:
  - Look-alike and sound-alike names
  - Look-alike packages, dosage ranges, umbrella ranges, dangerous devices, etc.


VU D'ÉVITER L'ÉVITABLE

Déconditionnement et reco

Deux signalements au Programme Prescrire "Éviter l'Évitable" montrent qu'en établissement de soins, l'absence de conditionnement unitaire expose à des erreurs.

Annual drug packaging review

- Established by *Prescrire*'s Packaging Working Group
- On the basis of the last year findings and observed trends, with special highlights as necessary
- Published in the March issue of the French journal
- Translated fully or partly for publishing in later issues of *Prescrire International*

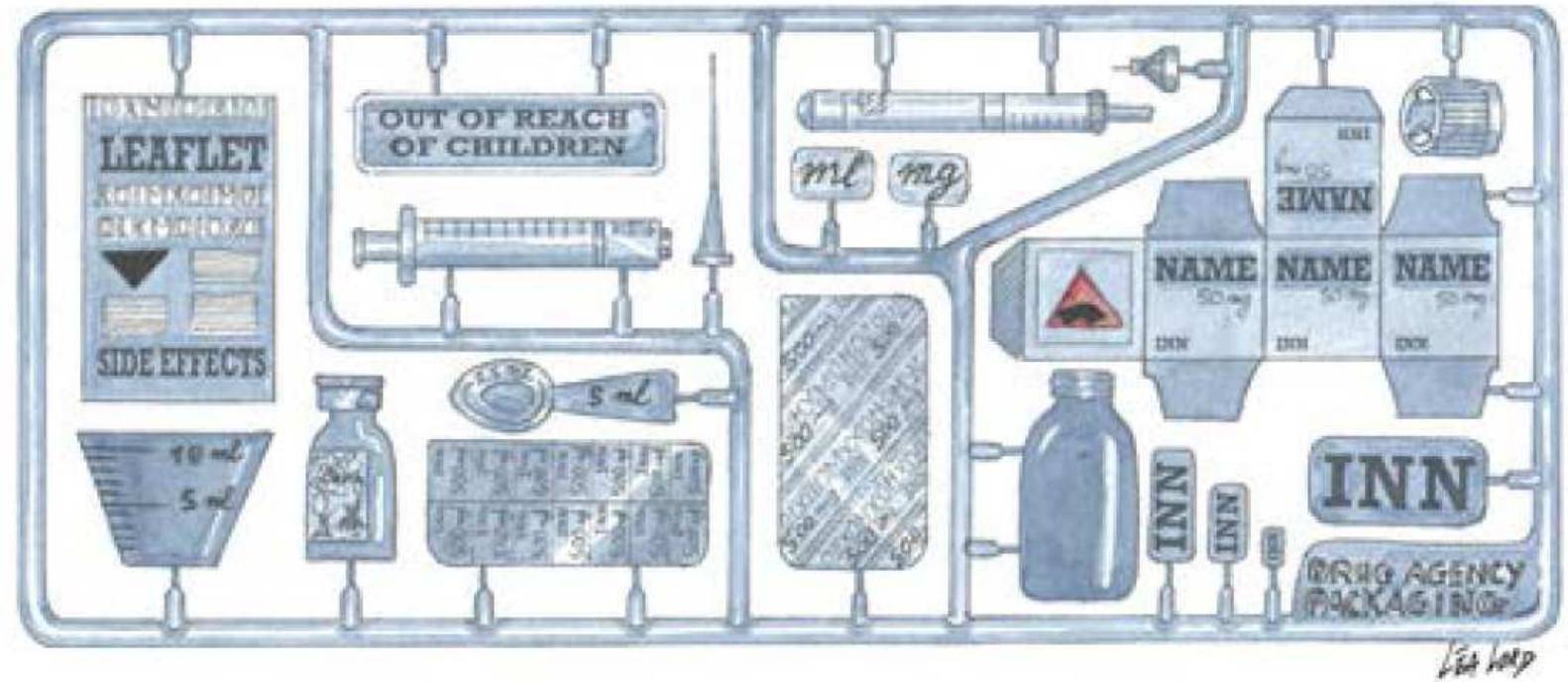
Prescrire Packaging Awards

- List prepared by the *Prescrire* Packaging Working Group
- Submited for internal review and discussed during a preparatory meeting of the editorial team
- Granted to the compagnies during the annual *Prescrire* **Golden Pill Award**

- The **Packaging awards** highlight the interest of a packaging for the patient or the healthcare givers

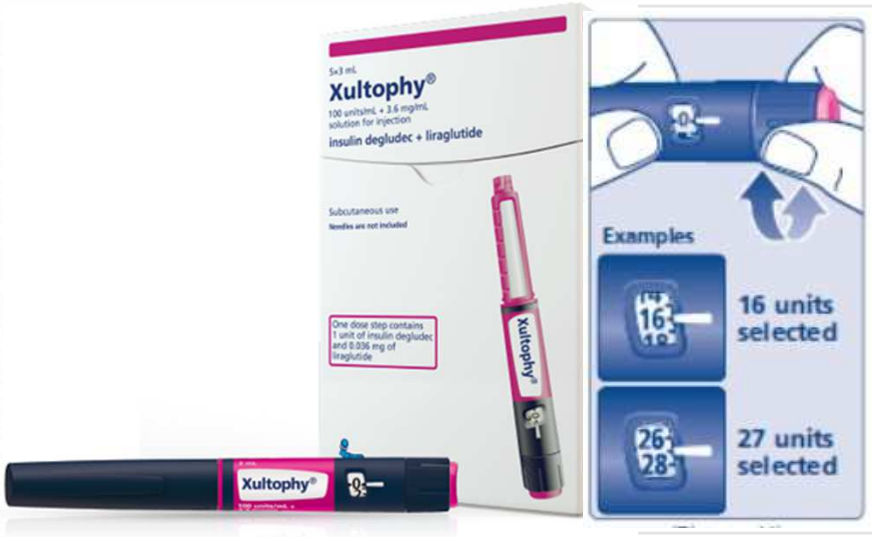
- The **Red and Yellow Cards** drive attention to dangerous products prone to error or overdose

Findings from Prescrire packaging analysis



High-strength insulins: dose counter inaccuracies

- flouting the 1 unit step rule
  - 2 units steps (i.e. Tresiba Flextouch° 200 units/ml)
  - 0,5 units steps (i.e. Humalog Junior Kwikpen° 100 units/ml)
- malfonctionning on intermediary positions
  - blocking any administration
  - the pen's spring mechanism tends to wind back to the lower graduation
- confusing for visually impaired patients
- misleading display in the case of fixed dose combinations
  - i.e. 1 dose step of Xultophy° correspond to 1 unit of insulin degludec + 0.036 mg of liraglutide



Children at risk: still not enough child-proof cap

- 2011: 10 Red Cards
- 2012: 3 Red Cards
- 2013: 6 Red Cards
- 2014: 9 Red Cards
- 2015: 4 Red Cards
- 2016: 4 Red Cards
- 2017: 10 Red Cards
- 2018: 15 Red Cards

Oral methotrexate: room for improvement

- Replacing bulk bottles of tablets with blister packs represents progress
  - risk of spilling the tablets
  - contamination by scattering powder from the tablets.
  - easy opening of the bottle facilitates ingestion by a child
- In France, Methotrexate Bellon° and Imeth° still packaged in bulk bottles without safety caps
- More substantial improvement is possible (see also IMSN members response to the EMA consultation)
  - child resistant film on the blister packs
  - providing a tablet-extracting tool for patients whose hands are affected by rheumatoid arthritis
  - pre-perforated blister packs which allow each tablet to be identified
  - roots causes not to be overlooked: regulation, packaging, labelling and awareness

Novatrex° (methotrexate) analysed end 2017

Methotrexate Bellon° analysed in 2018

http://english.prescrire.org/en/79/207/46302/5679/5562/SubReportDetails.aspx

Unit-dose blister packs: too rare in community pharmacies

- low-quality blister packs

  the detached portion of the blister pack for a dose rarely displays all the information required for safe dosing, in particular the INN and dose strength

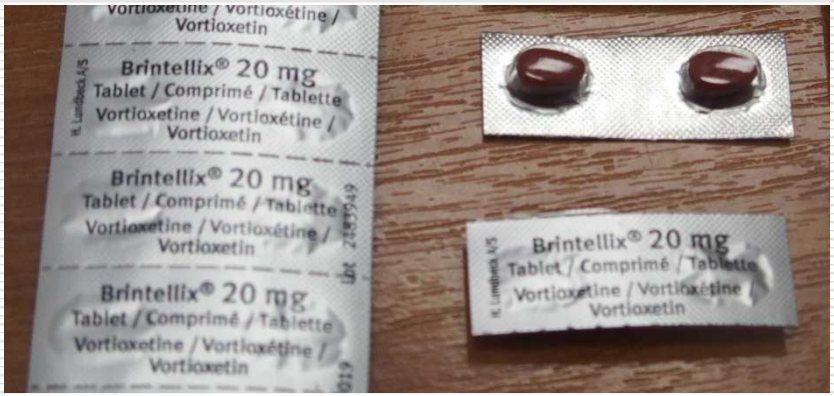
- vortioxetine (Brintellix°)

  Perforated blister pack, with each section containing two blisters with one tablet each

  Just one label per perforated section

  In this labelling, does the 20 mg of vortioxetine correspond to 1 tablet or 2 tablets?

  An overdose was reported in 2004, due to this type of packaging with Néoral° (ciclosporine)



Dosing devices: an area that needs work

- Too many dosing devices are imprecise (cup, dropper, etc.) whereas there are oral syringes that are well adapted
- Too many dosing devices and COPE are calibrated in milliliters as opposed to milligrams of the drug, although the latter is possible
- Two dosing devices in the same box = danger
- Dosing devices needed for topical drugs, etc.

Adverse effects in patient leaflets: recurrent shortcomings

- Known harms omitted from the SPCs and patient leaflets of both new and older drugs
- Insufficient prioritisation of adverse effects

  idebenone (Raxone°): ▼ present whithout advice for monitoring hepatotoxicity
- Omissions and failure to update the documentation of older drugs
  - Not all vaginal drugs containing estriol alert on risks of arterial or venous thrombosis and breast or endometrial cancer
  - Cutaneous retinoids available in France, adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene, and risks of teratogenicity: failing to mention the need for effective contraception
- Patients discouraged from reading about adverse effects

  long lists of adverse effects not written to provide information to patients, but rather to protect pharmaceutical companies from litigation
- Leaflets must accurately reflect the information given to healthcare professionals in the latest version of the SPC.

Lobbying for safer packaging

http://english.prescrire.org/en/79/549/49235/3722/3480/SubReportDetails.aspx

Where to find our position papers?

http://english.prescrire.org/en/79/549/49235/3673/ReportDetails.aspx

Prescrire IN ENGLISH

Stay connected to
our packaging analysis procedures at english.prescrire.org

THANK YOU!