A look back at 2008: pharmaceutical quality problems

Twelve-five (50%) of the 50 new brand name products introduced to the market in France that we examined in 2008 were designed to treat cancer, HIV infection or rare diseases. None represented a major therapeutic advance. Line extensions making treatment more convenient included methadone capsules and a liquid form of metformin.

Marketing authorisation does not provide sufficient guarantees of safety and effectiveness. In 2008 we rated 23 new products as “Not acceptable” and advised our readers to avoid them.

Drug regulatory agencies were reluctant to take the necessary measures, such as refusal to grant marketing authorisation, to protect patients from exposure to drugs with negative risk-benefit balances.

Serious incidents involving contamination of certain batches of nelfinavir and heparin are reminders that the pharmaceutical industry needs to maintain the highest quality standards.

Drug prices remain high and bear little relation to therapeutic benefits.

It is now clear that direct drug advertising to the public and healthcare professionals has negative public health consequences. However, it has not yet been banned.

In summary, deregulation continued in 2008. Only by maintaining pressure on the authorities and regulatory agencies can patients and healthcare professionals resist these negative trends.

In 2008, we published independent assessments of about 300 products (a), including 87 new products: 50 products with new brand names, 20 line extensions; and 17 copies with invented brand names. The following is an overview of the major trends observed in 2008.

Little therapeutic advance

In 2008 we examined 120 new products and indications. Nearly half of new products (n=57) provided no significant advantages over existing options.

The large number of drugs that we rated as “Unacceptable” or “Judgement reserved” highlights the inability of regulatory agencies to ensure the safety and efficacy of the products they allow on to the market.

New products: mainly for cancer, HIV infection and rare diseases. Half of the 50 new brand name products that we examined in 2008 were intended for 3 major disease categories. Some drugs improved patient management, but none represented a major therapeutic breakthrough:

- 13 were for cancer (see la revue Prescrire 303 p. 27-30);
- 4 were for HIV infection (see la revue Prescrire 303 p. 42);
- 8 were for rare diseases (other than cancer) (see la revue Prescrire 303 p. 43).

No real therapeutic advance in patient care. Among the new indications and products (new brand names and line extensions) that we exam-
New products and market withdrawals reported in *Prescrire* over the last 10 years (a)

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<td>40</td>
<td>18</td>
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<td>39</td>
<td>34</td>
<td>37</td>
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<td>23 (e)</td>
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<td>presented to general practitioners and/or specialists</td>
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<td>37</td>
<td>32</td>
<td>37 (22)</td>
<td>56</td>
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<td>77 (46)</td>
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<td>3 (g)</td>
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<td>Market withdrawals for pharmacovigilance reasons</td>
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<td>216</td>
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**Prescrire’s ratings of new products and indications over the last 10 years (a)**

- Including market withdrawal of 11 products containing 100 mg of *Buflomedil* in November 2006 and reported in the *la revue Prescrire* in January 2007.
- Including 9 not yet marketed on 2 January 2009.
- Including 2 not yet marketed on 2 January 2009.
- Including 2 reported in the *la revue Prescrire* 303 (January 2009).

### Prescrire’s Ratings of New Products and Indications over the Last 10 Years (a)

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<td>84</td>
<td>135</td>
<td>141</td>
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</tbody>
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### Notes

- For reasons of space, this table only gives the results for the last 10 years. The results for previous years (1981 to 1998) can be found in *Prescrire* 213 p. 59 and 224 p. 56.
- This table includes new products (except for copies) and indications presented to physicians and pharmacists by drug companies for use in the community or in hospitals, and, since 2005, line extensions (new doses, new forms and presentations of existing drugs), and products for pharmacists advice and self-medication that were rated in these pages. A product is counted several times if it received different ratings in its different indications.
- Including 2 jointly marketed products.
- Namely:
  - hydroxyzine for some patients with sickle-cell disease (*la revue Prescrire* 296).
  - methotrexate in type 2 diabetes (*Prescrire International* 98).
  - methadone capsules for opiate replacement therapy (*la revue Prescrire* 295 and coming in *Prescrire International*).
  - raltegravir for HIV-infected patients with multiple treatment failure (*Prescrire International* 96).
  - sorafenib in liver cancer (this issue page 59).
  - melphalan for unblocking thromosed central venous or dialysis catheters (*la revue Prescrire* 302 and coming issue of *Prescrire International*).
- Including 2 products targeting the public and rated “Caution”.

### The lamivudine-zidovudine fixed-dose combination simplifies treatment of HIV infection (*la revue Prescrire* 296 p. 414).

### The risk-benefit balance of dantrolene in patients with cerebral palsy is uncertain (*Prescrire International* 98), as is that of infliximab in severe Crohn’s disease (*Prescrire International* 96).

### The tendency to grant multiple new indications for existing psychotropics is disturbing; for example, fluoxetine for depression in children over 8 years of age (*Prescrire International* 97) and hydroxyzine for patients who have trouble falling asleep (*la revue Prescrire* 291 p. 7).
Drug evaluation: agencies must do more to protect patients

The growing tendency for drugs to be marketed prematurely, without adequate assessment, is particularly troubling, but not, apparently, for the drug licensing authorities. The losers are the patients who are exposed to drugs that are no better than existing options and that may be more harmful.

Waivers mean faster profits but more risks for patients. The European Union offers drug companies a variety of waivers that help them get their products on the market more rapidly: conditional marketing authorisation, exceptional marketing authorisation and accelerated assessment (Prescrire International 99).

An American study has shown that more rapid processing of marketing authorisation applications, either as a result of pressure from drug companies or from patients demanding early access to certain treatments, is associated with more frequent major post-marketing alerts and with more drug withdrawals for safety reasons (la revue Prescrire 297 p. 535).

Thus, among the 6 drugs granted waivers to the standard authorisation procedure by the EMEA that we examined in 2008, we considered three to be “Not acceptable”: panitumumab (conditional marketing authorisation), irudisulfase (exceptional marketing authorisation) and trabectedin (exceptional marketing authorisation). Only one drug, raltegravir (conditional marketing authorisation), was useful for patients.

Public trial registries are needed. More transparency is needed in clinical evaluation of drugs, whether the results are positive or negative, in order to assess the risk-benefit balance of new products. Mandatory inscription of all drug trials, and their results, in a public registry is one means of achieving this goal. This would also limit data misrepresenting and manipulation, as in the celecoxib scandal in the early 2000s (la revue Prescrire 297 p. 536-534).

It is better to refuse marketing authorisation in the first place. It is better not to license a product rather than see it withdrawn later for safety reasons. In 2008 the European Medicines Agency demanded the market suspension ofrimonabant only 2 years after authorising its use in obesity, despite an unfavourable risk-benefit balance (la revue Prescrire 302 p. 885, 897 and 909). The Agency also demanded the market suspension of lonsytrone, an iontophoretic transdermal system deliveringfentanyl, which had been authorised despite evidence of unreliable drug delivery (la revue Prescrire 303 p. 19). Marketing authorisation of inhaled insulin was also withdrawn, at the company’s request; here too, the data submitted for marketing authorisation were clearly negative at the time of approval (la revue Prescrire 291 p. 16). If the Agency had refused to approve these three products in the first place, it would have prevented the unnecessary exposure of patients to a risk of serious adverse effects.

We were relieved to see the withdrawal of marketing applications for the psychotropics desvenlafaxine (in hot flashes associated with menopause) and duloxetine (in fibromyalgia), after the European Committee for Medicinal Products for Human Use (CHMP) issued negative opinions (la revue Prescrire 300 p. 737-738; la revue Prescrire 303 p. 15).

Withdrawals of marketing authorisation: too rare. The above examples show that the Committee for Medicinal Products for Human Use (CHMP) is capable of “doing the right thing”. Hopefully, national agencies will follow their lead. Unfortunately, some drugs are still marketed in France despite a clearly unfavourable risk-benefit balance. These drugs include: benfluorex, an amphetamine used as an adjuvant to dietary measures in diabetic patients (la revue Prescrire 291 p. 19); celecoxib, a NSAID used in rheumatology (la revue Prescrire 291 p. 13); and meprobamate, a psychotropic used in alcohol withdrawal (la revue Prescrire 292 p. 100).

In September 2007 we asked the CHMP to arbitrate in the case of the analgesic combination containing dextropropoxyphene and paracetamol, which had already been banned in several European countries. On 2 January 2009, the CHMP’s conclusions had still not been made public (la revue Prescrire 294 p. 259).

If this situation is to improve, patients and healthcare professionals will have to take it upon themselves to counteract the excessive influence of Big Pharma.

Biosimilars: in practice, simple copies. In 2008 the first “biosimilar” epoetins were marketed in France. Binocrit (epoetin alfa; Prescrire International 99) and Abseamed (epoetin alfa; la revue Prescrire 303 p. 20) are both considered biosimilar to Epresc (epoetin alfa). They cannot be dispensed interchangeably from French community pharmacies, but they are still nothing more than simple copies. Their efficacy and adverse effects are identical, irrespective of the product and international nonproprietary name (INN).

Generics: only some are welcome additions. In 2008 we examined 26 new generic versions of existing products in France. About one-third of them are useful for patients.

Other generics should be avoided, whatever their cost. Examples include bicuxatamide in advanced-stage or metastatic prostate cancer and venlafaxine in various psychiatric disorders (depression, social phobia, generalised anxiety).

Regulatory agencies: too many half-measures

Regulatory agencies rarely resort to truly effective measures, such as market withdrawal, in order to protect patients. They are too often more concerned with protecting companies’ financial interests, and simply withdraw certain indications, modify the summary of product characteristics (SPC) or information concerning risks.

Market withdrawals: too few in 2008. Three products were withdrawn from the French market for safety reasons: – aprotinin, an antifibrinolytic drug associated with excess mortality (Prescrire International 97); – fentanyl iontophoretic transdermal system, an unreliable delivery system for this opiate (Prescrire International 95 and 96); – rimonabant, a cannabinoid derivative used as an appetite suppressant, with numerous and sometimes fatal psychological effects (this issue p. 61).

This is too little, considering that many drugs, including some very old drugs, remain on the market despite unfavourable risk-benefit balances (see inset left).

Restricted indications: far less effective than simple market withdrawal. The restrictions placed on the indications for piroxicam, a nonsteroidal antiinflammatory drug (NSAID) used in rheumatology, are insufficient. Patients continue to be exposed to this drug’s adverse effects, while other safer NSAIDs are available (la revue Prescrire 294 p. 257).
The indication for “hypertriglyceridaemia” was removed from the benfluorex summary of product characteristics, but it is unacceptable that diabetic patients should still be exposed to this amphetamine (Prescrire 291 p. 19).

SPC modifications: too little stress placed on adverse effects. Risks identified after market release are sometimes added to the SPC. However, these changes can be difficult for healthcare professionals to detect, and regulatory agencies fail to publicise them adequately. Examples include: patent blue V and anaphylaxis (in a coming issue); ethinylestradiol-etonogestrel vaginal rings that may be accidentally expelled (Prescrire 292 p. 103); hydrochlorothiazide, indapamide and photosensitisation (Prescrire 300 p. 378); manidipine and gingival hyperplasia (Prescrire 295 p. 341); and trospium and QT prolongation (Prescrire 295 p. 346).

Regulatory agencies provide limited information about risks. Regulatory agencies have a responsibility to inform users of the risks associated with specific drugs.

Some of the safety information disseminated by the European and French agencies was presented in these pages in 2008. Examples include: oesolamivir and gastrointestinal bleeding (Prescrire 293 p. 186); sirolimus and tuberculosis (Prescrire 294 p. 266); topical tacrolimus and cancer (Prescrire 301 p. 828); and varenicline and gastrointestinal, psychiatric and cardiovascular disorders (Prescrire 294 p. 266).

The limited safety information that does trickle down from regulatory agencies to the public is often inadequate. Prescrire had to ask the EMEA for access to important data that had been kept from the public. Examples include: oxenatide and renal failure (Prescrire 299 p. 664), sitagliptin and allergies (Prescrire 302 p. 907), and sorafenib and gastrointestinal perforation (Prescrire 299 p. 664).

**Pharmaceutical quality: vigilance needed**

Marketing authorisation offers certain guarantees in terms of pharmaceutical quality, as regulatory agencies inspect the production sites and impose controls during the manufacturing process. In contrast, other product categories such as dietary supplements, medical devices, and cosmetics, are less strictly regulated.

In 2008 the transposition of European Directive 2004/27/EC on drugs for human use into French law was nearly complete (Prescrire 303 p. 14). However, it will now be necessary to ensure that these provisions are properly implemented, in patients’ interests, and that any loopholes are not exploited.

**Transparency of French healthcare authorities: totally inadequate.** The 2004 EU Directive places certain obligations on the health authorities with respect to transparency. In particular, the authorities must publish the agendas and minutes of their committee meetings, as well as public assessment reports, and any conflicts of interest of committee members.

The French Health Products Safety Agency (Afssaps) does not always fulfil these obligations. Agendas are not made public and there is a delay in the publication of minutes, with no guarantee of exhaustiveness. In addition, marketing authorisation committee reports contain a bare minimum of information (Prescrire 303 p. 14).

The process of placing documents online has been very slow: on 31 December 2008, only 9713 summaries of product characteristics and about 100 assessment reports were available for 19 535 authorised products.

Agendas of the Transparency Committee of the French National Authority for Health (HAS) are placed online before meetings, but there is a delay in reporting the minutes and reports are often incomplete. The voting details on drug pricing are welcome, but the reports of the proceedings are often too brief.

**Pharmacovigilance in Europe: vigilance required.** In early 2008 the European Commission launched public consultations on some troubling proposals concerning the organisation of pharmacovigilance in Europe (Prescrire International 99 and www.prescrire.org). In particular, the Commission proposed to simplify pre-marketing assessment procedures and to make the drug companies responsible for pharmacovigilance. Some of these unwelcome proposals were dropped in the face of public mobilisation. We will continue to monitor the situation.

**Patient “information” provided by drug companies: massive opposition from health stakeholders.** In 2007 and 2008 the European Commission launched several public consultations with the ultimate goal of allowing drug companies to communicate directly with the public on the subject of prescription drugs (see www.prescrire.org). Almost all healthcare stakeholders in Europe opposed these proposals.

Each stakeholder has a specific role to play. The role of drug companies is to discover, develop and manufacture useful new drugs of the highest pharmaceutical quality (including high-quality packaging). BigPharma should have no say in treatment choices.

**Drug pricing: no relation to therapeutic benefits.** In 2008 the prices of new drugs continued to bear little relation to the therapeutic advantage provided to patients.

**Ever higher prices.** Examples include the £2000 price granted for dexrazoxane treatment of anthracycline extravasation in France, even though this drug had no proven advantages over existing options (Prescrire International 97); and the €35 000 per month for idersulfase therapy for a child with mucoplycosacharidosis type II who weighs 30 kg, even though the benefits of this recombinant enzyme...
A wide gap between healthcare provision and patients’ needs

Much remains to be done to protect patients from needless exposure to potentially harmful drugs, and to facilitate access to care for those who truly need it.

Medication of existence: specific rules needed. There is a growing trend towards the “medication of existence”. Examples include psychotropics for children (la revue Prescrire 296 p. 410-411), drugs for hot flashes in post-menopausal women, and treatments for fibromyalgia (la revue Prescrire 300 p. 725). The growing market in products for self-medication encourages people to take drugs even when drugs are not necessary (la revue Prescrire 293 p. 217; la revue Prescrire 299 p. 653-654).

Faced with this growing pressure, the French authorities should compensate pharmacists based on the quality of advice they provide, and not only on the volume of drugs they sell (la revue Prescrire 301 p. 801).

What patients need from healthcare professionals is time, time to be heard and time to learn, and not just some illusory panacea.

Difficult access to some treatments. Some medical treatments can be difficult to obtain in France, and not just because of cost.

Access to methadone capsules for opiate replacement therapy is particularly complicated. This is a shame after having waited so many years for this more convenient treatment (la revue Prescrire 296 p. 422).

The time limit for the use of mifepristone for pregnancy termination rose from 7 to 9 weeks of gestation, but only in healthcare institutions. Access to abortion is still too difficult in France, mainly due to the insufficient number of physicians authorised to practice drug-induced termination, and sometimes also due to lengthy delays in patient management (la revue Prescrire 291 and 302).

“Morning-after contraception” is difficult to obtain in some pharmacies (la revue Prescrire 300).

Advertising: just ban it!

Drug advertising is a classic way of boosting sales and extending off-label use.

Advertisements and vaccines: arrangements in companies’ interests. Direct-to-consumer advertising is forbidden in France for reimbursed and prescription-only drugs, with the exception of vaccines and products used in smoking cessation.

Direct-to-consumer advertising of vaccines must comply with the recommendations of the French Technical Committee on Vaccination. However, these recommendations are often difficult to convey in brief advertising messages. The authorities therefore “adapted” the relevant regulation, authorising vaccine advertisements to carry abbreviated recommendations, instead of simply banning these ads (la revue Prescrire 300 p. 737).

Loopholes. Companies use a variety of tactics to get around the ban on direct-to-consumer advertising for prescription-only and reimbursed drugs, including gadgets such as pens, paperclips, notebooks (la revue Prescrire 291 p. 735). “Information” in the form of press releases for journalists (la revue Prescrire 300, inside back cover) and publication of articles in the lay press concerning certain diseases and their treatment (la revue Prescrire 302 p. 948) are other ways for drug companies to stimulate demand for specific drugs.

Ads targeting healthcare professionals: still too many abuses. The tendency of companies to influence the education of healthcare professionals is growing, and periodicals with financial links to the pharmaceutical industry continue to be published (la revue Prescrire 291, inside back cover; la revue Prescrire 297, inside back cover, la revue Prescrire 299; inside back cover). The “information” disseminated by drug companies is in no way conducive to high-quality care. In 2008, we reported 16 advertisements aimed at healthcare professionals that were banned in France (la revue Prescrire 292 p. 99; la revue Prescrire 294 p. 259; la revue Prescrire 299 p. 657-658; la revue Prescrire 302 p. 899). The French Agency (Afssaps) imposed most of these bans for the promotion of off-licence indications.

Healthcare professionals must remain vigilant and refuse to put their education in the hands of Big Pharma.

Ban all drug advertising! Studies of the two countries that authorise prescription drug advertising (United States and New Zealand) show that it has a negative impact on public health and healthcare spending. In addition, the authorities have been unable to control this advertising. Advertising and other forms of “information” provided by drug companies lead to overconsumption of certain drugs and to questionable treatment choices (la revue Prescrire 291 p. 63-64). “Information” provided to healthcare professionals by drug companies, mainly through pharmaceutical sales reps, is not only of poor quality but also very costly for society (la revue Prescrire 299 p. 704-705).

Banning all drug advertising is the only way of protecting the public from its harmful effects.

The authorities must take action

The authorities have the means to take action, for example by the equitable distribution of available resources, in patients’ best interests, and by taking into account real development costs and therapeutic benefits when setting the price for new products. Yet deregulation continued in 2008.

Healthcare professionals and patients who are interested in high-quality care must maintain the pressure on the healthcare authorities and, while awaiting a real therapeutic breakthrough, they must make the best use of essential drugs.

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