New drugs and indications in 2010: inadequate assessment; patients at risk

In 2010, we rated 97 new drugs or new indications in our French edition *la revue Prescrire*, only 4 of which provided a therapeutic advantage. However, 19 others (1 in 5) were approved despite having more harms than benefits.

More paediatric products were released in 2010 than in previous years, but few of them made any real difference and many had not been properly evaluated.

Drug regulatory agencies can protect patients from exposure to dangerous drugs by refusing to grant market approval or by demanding their market withdrawal. Yet they are failing to fulfil this responsibility: so-called risk management plans and modifications to the wording in the SPC are only half-measures.

Too often the authorities put companies’ short-term financial interests above patients’ well-being by granting premature marketing authorisation, by agreeing to high levels of reimbursement that fail to take added therapeutic value into account, and by allowing the development of “umbrella” ranges.

The European authorities’ questionable plans for pharmacovigilance and advertising of prescription-only drugs were restricted after public mobilisation, but they are still likely to undermine healthcare quality.

Decision-makers must make patients’ well-being their top priority.


In 2010, our independent analyses of 291 new drugs and indications were published in our French edition *la revue Prescrire*. They included: 46 new products with new brand names, 17 line extensions, and 24 copies with fancy brand names (“hidden generics”) (a).

All that glitters...

We systematically examine the therapeutic value of all new drugs, products with new brand names, line extensions, and new indications of existing products in France. In 2010, we rated 97 drugs, including 3 products that we re-examined after longer follow-up. ⬤

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In addition: new indications, reassessments (“A second look”) for drugs already analysed in Prescrire, generics, wording changes in the labelling, miscellaneous changes, brand name changes, and market withdrawals.
New drugs and indications in 2010

In 2010, certain drugs represented a slight therapeutic advance (rated as “Possibly helpful”), but their assessment was usually minimal and sometimes wholly inadequate. They included:

- darunavir (Rev Prescrire n°321) and tipranavir (Rev Prescrire n°321) for HIV-infected children;
- fosartan for hypertensive children (Prescrire Int n°108);
- omeprazole in heartburn and gastropathic reflux, and Helicobacter pylori infection (Rev Prescrire n°319);
- the combination of peginterferon alfa-2b and ribavirin in hepatitis C (Rev Prescrire n°325);
- botulinum toxin type A for limb spasticity (Rev Prescrire n°325).

Monoclonal antibodies: too many products, rarely helpful. The number of therapeutic monoclonal antibodies (whose international non-proprietary names (INNs) end in -mab) and their indications continue to grow, especially in oncology and rheumatology. These drugs are publicised as “targeted treatments” heralding an era of “personalised medicine”. In practice, they rarely represent a major therapeutic advance, and several expose patients to unjustified risks (see notes d and e of the rating table below).

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### Prescrire’s at-a-glance rating

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- a- For reasons of space, this table only shows the results for the last 10 years. The previous years’ results (1981 to 2000) can be found in Prescrire Int n°58. This table shows new products (other than generics copies) and new indications proposed by drug companies to physicians and pharmacists, for use in hospitals and/or the community; and, from 2005 onwards, line extensions (new dose strengths, new form/presentations of existing drugs) and products for self-medication, rated in our French edition la revue Prescrire. A given product is counted several times if it was rated differently in its different indications.
- b- Including two jointly marketed products.
- c- Imatinib reassessed in inoperable or metastatic gastrointestinal stromal tumors (Prescrire Int n°114).
- d- The drugs were:
  - acazipam in periodic syndrome in combination with cryoprine (Prescrire Int n°324);
  - Japanese encephalitis vaccine (Prescrire Int n°106).
- e- The drugs were:
  - fixed-dose combination of amlopidine + valsartan + hydrochlorothiazide (Prescrire Int n°114);
  - bevacizumab in metastatic breast cancer (Rev Prescrire n°317);
  - capsaicin patches for neuropathic pain (Rev Prescrire n°318);
  - cetuximab in colon cancer (Rev Prescrire n°324);
  - duloxetine for prevention of recurrent depression (Prescrire Int n°111); histamine in acute myeloblastic leukaemia (Rev Prescrire n°321).
  - ibivadine in stable angina (Prescrire Int n°111);
  - long-acting injectable elancapazine in schizophrenia (Prescrire Int n°107);
  - omalizumab in severe persistent asthma in children (Rev Prescrire n°324);
  - zolmitriptan in the first-line treatment of migraines (Rev Prescrire Int n°110);
  - mifamurtide for osteosarcoma (Rev Prescrire n°326);
  - pazopanib in kidney cancer (Prescrire Int n°114);
  - sildenafl (Prescrire Int n°109) and tadalafil (Rev Prescrire Int n°321) in stage II (mild) pulmonary hypertension;
  - tosirimus in mantle cell lymphoma (Prescrire Int n°111);
  - trastuzumab in oestrogen receptor positive breast cancer (Rev Prescrire n°326);
  - vinflunine in bladder cancer after failure of first-line cisplatin-based treatment (Prescrire Int n°112).
- f- The drugs were:
  - autologous chondrocytes in autologous chondrocyte grafting for knee cartilage damage (Rev Prescrire Int n°326);
  - imatinib as an adjuvant to surgical excision of gastrointestinal stromal tumors (Prescrire Int n°113);
  - siprotroprin in tetrohydrobiopterin deficiency (Rev Prescrire n°316).
Avoiding iatrogenic complications

Marketing authorisation is being granted prematurely for an increasing number of new drugs, before their efficacy and particularly, their adverse effects have been properly evaluated (Rev Prescrire n°326).

One would expect drug regulatory agencies to be more cautious and responsive following scandals such as the diethylstilbestrol (DES) disaster and, more recently, the benfluorex (ex-Mediator®) affair (Prescrire Int n°105, 107, 113 and Prescrire website).

Market withdrawal: an effective measure, especially when timely. Drug regulatory agencies often appear reluctant to withdraw drugs with negative risk-benefit balances, allowing sales to continue unabated and needlessly exposing patients to a risk of adverse effects.

The return of topical ketoprofen to the market after initial withdrawal at the demand of the French drug agency (Afssaps) illustrates how drug companies’ financial interests are often put ahead of patient safety (Prescrire Int n°109, 112, 113). In 2010, only a small proportion of drugs with a negative risk-benefit balance were taken off the market, several years after their dangers were first identified. They included bufexamac, a topical non-steroidal anti-inflammatory drug, because of potentially serious cutaneous disorders (eczema) (Rev Prescrire n°321, 325); carbocisteine and acetylcisteine (mucolytic agents) in infants, because of respiratory adverse effects (Rev Prescrire n°320, 324); rosiglitazone (an antidiabetic), because of cardiovascular adverse effects (Rev Prescrire n°325, 326); and sibutramine (an appetite suppressant), also because of cardiovascular adverse effects (Prescrire Int n°107).

Refusal to grant marketing authorisation: another effective means of protecting patients. Patients were protected from exposure to unnecessary risks of certain drugs last year, after the EU Committee for Medicinal Products for Human Use (CHMP) refused to grant market approval or issued an unavourable opinion, leading the company to withdraw its application. They included:

- refusal of marketing authorisation for gemfloxacin, a particularly risky fluoroquinolone (Rev Prescrire n°319);
- refusal of marketing authorisation for ixabepilone in breast cancer, because of serious and frequent neuropathies and haematological disorders (Rev Prescrire n°315);
- refusal of extension of the indications for two psychotropics used in fibromyalgia: pregabaline and milnacipran (in depressions) (Rev Prescrire n°320).

Adverse effects: insist on more openness. Because marketing authorisation is increasingly granted prematurely, the adverse effect profiles of many new drugs are not properly documented at the time of market release. Post-marketing data on adverse effects are therefore crucial and must be made available to the public. The European Medicines Agency (EMA) issued alerts on the following products (among others) in 2010:

- ropinirole in restless legs syndrome: this dopamine agonist has known adverse effects but no proven efficacy in this setting. In 2010, the French authorities recommended that it no longer be reimbursed (Rev Prescrire n°325);
- telithromycin, a macrolide carrying a risk of cardiac, hepatic and visual disorders (Prescrire Int n°106 and www.english.prescrire.org);
- trimetazidine, because of a negative risk-benefit balance in angina pectoris, dizziness, tinnitus and visual disorders, and especially a risk of extrapyramidal syndrome and thrombocytopenia (Prescrire Int n°106 and www.english.prescrire.org).

On 21 December 2010, the fixed-dose combination containing dextropropoxyphene and paracetamol was still on the market, but it is slated for European market withdrawal in 2011 (on 1 March 2011 in France) (Rev Prescrire n°323 and www.english.prescrire.org).

Cost of inadequate regulation. In view of these few examples, how can decision-makers and health authorities be trusted, when they allow patients to be exposed to harmful drugs, letting society pick up the tab for hospitalisation, sick leave, and agree to provide reimbursement for vastly over-priced drugs. For example, the direct cost of prescriptions for glitazones in France was about 50 million euros in 2007, for the national health insurance system alone (Rev Prescrire n°317).

There is a cost for inadequate regulation. Decision-makers can start to get a grip on health spending by refusing to provide reimbursement for drugs with a negative risk-benefit balance.©Prescrire
Medicines agencies too often under the influence of drug companies

Drug regulatory agencies are responsible for protecting patients, notably by assessing drugs before they are allowed on to the market. Yet in 2010, the European agency (EMA) and EU member states’ agencies, including the French agency Afsaps, often failed to fulfil their responsibilities.

At a broader international level, the norms dictated by ICH (International Conference on Harmonisation) also fail to make patient safety their priority. It is this organisation, composed of representatives from the wealthiest countries’ drug regulatory agencies and 3 drug company trade associations, that sets the rules governing market access for new drugs (Prescrire Int n°108).

When agencies disagree, drug companies benefit. Drug regulatory agencies in various countries sometimes come to different decisions concerning approval of a specific drug: one country might wish to withdraw a risky drug, while others will insist on keeping it on the market. There is no valid reason why this should benefit the company rather than patients. Several such situations arose in 2010.

Rosiglitazone was withdrawn in the European Union but not in the United States, where the authorities simply demanded modifications in the wording of the SPC (Prescrire Int n°325 and www.english.prescrire.org).

Nimesulide was withdrawn from the market in Argentina, Belgium, Spain, Finland, Ireland, Singapore, etc., but not in all European Union member states. The CHMP even requested a study evaluating the hepatic risks in transplant centres, further delaying the decision on market withdrawal (Prescrire n°323 and www.english.prescrire.org).

Parecoxib was withdrawn from the Swiss market and rejected by the US Food and Drug Administration (FDA), yet it is still authorised in the European Union (Prescrire Int n°109).

Maraviroc has been authorised for first-line treatment of HIV infection in the United States, but not in the European Union, where the authorities justifiably consider that the assessment is inadequate (Prescrire Int n°110).

Agencies still grant marketing authorisation despite inadequate data. Accelerated marketing authorisation based on partial data may be justified when patients have no other treatment options and might reap a major benefit. But drug regulatory agencies increasingly approve new drugs on the basis of scant data, without demanding a comparison with an existing reference treatment. It sometimes seems that marketing authorisation is granted as a consolation prize for companies that have submitted multiple applications in various indications.

Tolvaptan was authorised for the syndrome of inappropriate antidiuretic hormone secretion, with no proof of efficacy, although the company had initially applied for an indication in heart failure (Prescrire Int n°109).

Gefitinib was authorised for some lung cancers on the basis of a minimal analysis showing no increase in survival (Prescrire Int n°107).

After unfavourable opinions issued by the FDA and EMA based on data presented in 2005, the EMA finally authorised dronedarone in atrial fibrillation, despite the lack of convincing data (Prescrire Int n°108).

Trials of raltegravir in first-line treatment of HIV-infected patients were not designed to show a benefit versus effective anti-retroviral combinations (Prescrire Int n°110).

The assessment report on vinflunine in bladder cancer states that the CHMP authorised this drug on the basis of a majority decision with many dissenters (Prescrire Int n°112).

Opacity: bad habits die hard. Once again in 2010, Prescrire deplored regulatory agencies’ lack of transparency.

In particular, the EMA refused to provide us with data used for the reassessment of topical ketoprofen gels. We filed a complaint with the European ombudsman (see www.english.prescrire.org).

Some of the documents obtained by Prescrire had been extensively blacked out, masking information of public interest. For example, sales figures and the number of reports of severe allergic reactions to phloroglucinol were blacked out by the French agency (Prescrire n°316). Certain pages of the report on excessive weight loss linked to exenatide were blacked out by the EMA, simply to protect the company’s commercial interests (Prescrire Int n°321).

In the United States, the FDA’s complicity towards a drug company that had failed to publish unfavourable clinical data on quetiapine, a neuroleptic, was revealed during legal proceedings initiated by the patients concerned (Prescrire Int n°112).

Conflicts of interest: too many experts with ties to drug companies. The French agency contracts outside experts to assess marketing applications. In late 2009, it published a review of how conflicts of interest were handled within the agency. This report revealed that regulatory obligations were not fully respected; in particular, more than half of the experts were not required to leave meetings in which they had a major conflict of interest (Prescrire Int n°108). These findings highlight the need for independent experts.

In 2010, the pharmaceutical industry was still heavily involved at every step of drug evaluation. And the fact that drug regulatory agencies are largely funded by drug companies (to the tune of 80% in the case of the EMA) rules out the likelihood of objective assessment (Prescrire n°319). European citizens must fight for the independence of drug regulatory agencies from the pharmaceutical industry.

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Inadequate “risk management” plans. “Risk management” plans and “risk minimisation” measures are frequently inadequate. They are often delegated to drug companies by drug regulatory agencies, and they mainly serve to justify premature marketing authorisation with a commitment to conduct large post-marketing trials (Rev Prescrire n°319).

Heterogeneous “umbrella” ranges: caution

In France, the self-medication market continued to grow in 2010, but most new products had little if any efficacy and did have noteworthy adverse effects. In addition, the fancy brand names and packaging concocted by manufacturers and allowed by drug agencies are unlikely to promote rational use. Pharmacists must carefully select the self-medication products they sell to their clients.

New self-medication products: amorolfine and omeprazole sometimes useful. In 2010, five drugs became available without a prescription: amorolfine (Rev Prescrire n°319), levo-cabastine (Rev Prescrire n°320), omeprazole (Rev Prescrire n°326), ivermectin (Rev Prescrire n°320) and trimethobutine (Rev Prescrire n°326).

Some provide a small benefit:
- amorolfine (Rev Prescrire n°321) is only applied once a week for fungal nail infections, instead of once a day as with ciclopirox;
- omeprazole (Rev Prescrire n°326) is the standard proton pump inhibitor for gastroesophageal reflux.

In contrast, ivermectin, a steroid, should not be used for sore throat (Rev Prescrire n°320).

Fancy brand names and “umbrel-la” ranges: misinformation and danger. Patient safety can be improved by highlighting the INN on drug labelling or including it in the brand name, thus reducing the risk of overdose with drugs present in several self-medication products, such as paracetamol and ibuprofen. This can also help to avoid confusion between similar brand names (Rev Prescrire n°318, 325).

In practice, the INN is rarely highlighted, particularly in self-medication products. “Umbrella” ranges, in which several products with a different composition or regulatory status share a common stem as part of their brand name, are proliferating. This creates a risk of confusion between drugs belonging to the same product line. This is especially the case for products sold to treat coughs and colds. For example, the following “umbrella” ranges were extended in France in 2010: Clarix® (Rev Prescrire n°318), Codotussyl® (Rev Prescrire n°317), Dolihume® (Rev Prescrire n°318) and Humex® (Rev Prescrire n°317).

Advertising: drug companies continue to spin their web

In late 2009, after reviewing the activities of medical sales reps, the French National Authority for Health (Haute autorité de santé, HAS) stressed the ineffectiveness of the medical sales charter, and admitted that it was incapable of regulating this activity (Rev Prescrire n°109). Although late in coming, this is a welcome realisation. In the meantime, however, drug companies continue to engage in advertising practices that put patients at risk.

Direct-to-consumer (DTC) advertising of prescription drugs: danger. The European Commission’s plans to allow companies to advertise prescription-only drugs directly to the public were once again debated by the European Parliament in late 2010 (see www.english.prescrire.org). The draft text was largely amended but still leaves the door open for some possible drug company advertising of prescription drugs to the public.

Marketing costs: nearly one-quarter of drug companies’ total spending. Patients and healthcare professionals need reliable and comparative information on illnesses and their management. Drug companies, for which each illness represents a market niche, are not in a good position to meet this need (Rev Prescrire n°324, 326). Yet marketing costs represent about 23% of drug companies’ spending, according to a survey conducted by the European Commission (Rev Prescrire n°315).

Drug promotion can take various forms, from training courses “under the influence” of the private sector (Rev Prescrire n°319), to the use of high-tech gimmickry to hide the dearth of real innovation (Rev Prescrire n°316), and advertising disguised as scientific information (Rev Prescrire n°323). Some healthcare professionals contribute indirectly to drug companies’ marketing strategies by providing information on prescriptions and sales, sometimes in return for small gifts (Rev Prescrire n°315).

Illicit advertising aimed at healthcare professionals. Doctors, pharmacists and even nurses are all targeted by drug companies seeking to increase sales of their products (Rev Prescrire n°108).
Finding solutions, along with patients

Faced with ongoing deregulation, with companies overstepping their roles, and with decision makers and health authorities who still fail to make patients’ interests their top priority, it is up to healthcare professionals to assure quality of care and maintain patient trust.

Training and education. Quality healthcare requires continuing education for healthcare professionals and reliable information for patients. This implies:

– basic education for all healthcare professionals in the principles of critical appraisal (Rev Prescrire n°320), so that they are in a position to analyse clinical assessment data on individual drugs, instead of relying solely on others’ judgement (Rev Prescrire n°321); it is particularly important to be able to distinguish surrogate endpoints from robust outcomes that take adverse effects into account (Rev Prescrire n°320);

– searching SPCs for important “buried” information such as clinical trial data and adverse effects (Rev Prescrire n°319);

– being able to recognise a drug’s pharmacological class, notably by using international nonproprietary names (INNs), in order to avoid exposing patients to known adverse effects (Prescrire Int n°108);

– reminding patients not to believe everything they read or hear in the media. Reports of research results in the lay media can be misleading: many researchers have a tendency to exaggerate the significance of their findings, both for financial reasons and for personal status (Rev Prescrire n°320);

– acknowledging one’s errors, as part of a constructive attitude towards improving professional practice (Prescrire Int n°109).

Mobilise! The positive impact that healthcare professionals and patients can have on healthcare quality was illustrated by several events in 2010:

– a French physician succeeded in bringing the severe adverse effects of benfluorex (ex-Mediator°) to the public’s attention (Rev Prescrire n°325 and www.english.prescrire.org), and a national health insurer (Cnamts) commissioned a study of its adverse effects (issue 316 p. 114), both of which led to benfluorex being withdrawn from the French market;

– patient groups successfully lobbied for market reinstatement of 100-mg capsules of efavirenz that are adapted to the treatment of certain HIV-infected young children (Rev Prescrire n°320).

Some of the advertisements banned by the French regulator (Afssaps) in 2010 are particularly informative:

– misleading comparison and overstated results for Alimta® (pemetrexed) and Loramyce® (miconazole) (Rev Prescrire n°318);

– minimisation of the risks of Botox® (botoxulinum toxin A) (Rev Prescrire n°318); overstated claims concerning the indications for Calcipray vitamine D3® and Caltrate vitamine D3® (calcium + vitamin D3), Gardasil® (papillomavirus vaccine 6, 11, 16, 18), Lacteo® (Lactobacillus acidophilus) and Solacry® (vitamin A + L cystine + sulphur + yeast) (Rev Prescrire n°318; 323; 326);

– misleading information on the indications for Inoler® (ferrous succinate) (Rev Prescrire n°318);

– unfounded criticism of generic versions of Omeclid® (tamsulosin) (Rev Prescrire n°318);

– overly positive presentation of Exlorge® (amlodipine + valsartan) and Tareg® (valsartan) by opinion leaders (Rev Prescrire n°323).

In the United States, legal action taken against the company marking quetiapine (Seroquel®) revealed the extent to which some firms are willing to go to promote their products: off-label promotion, financial incentives for physicians to write or even simply sign articles on off-label uses. The company was forced to refund public health insurers for the costs of unwarranted prescriptions (Prescrire Int n°112).

Resist “medicalisation of life”. Disease-mongering continued unabated in 2010, especially in the field of mental health (Rev Prescrire n°321 and www.english.prescrire.org). Thus, in draft version V of the Diagnostic and Statistical Manual (DSM), to be published in 2012, certain diagnostic criteria are bizarre and diagnostic thresholds for some illnesses have been lowered (Rev Prescrire n°323). In 2010, the indications for sertraline were extended to cover various anxiety disorders (panic disorder, social anxiety disorder, post-traumatic stress disorder) (Rev Prescrire n°316).

Companies are trying to get their products authorised for use in earlier stages of the disease concerned. For example, glatiramer is now authorised for suspected recent-onset multiple sclerosis (Prescrire Int n°108). This medicalisation serves companies’ interests by expanding the market for their drugs, at the expense of patient safety and well-being.

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Patients first!

In 2010, as in previous years, there was a dearth of real therapeutic advance as well as continued failings of policy makers and healthcare authorities, such as approval of poorly evaluated drugs with negative risk-benefit balances, or failure to withdraw them from the market.

Unable to rely on regulatory agencies and healthcare authorities, it is up to healthcare professionals to select drugs that truly benefit their patients and avoid needlessly exposing them to the risk of adverse effects.

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