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# A REVIEW OF NEW DRUGS IN 2004

## Floundering innovation and increased risk-taking

● In 2004 the number of new medicines released onto the French market was similar to the number released in previous years, but there were fewer and less definitive therapeutic advances. Rofecoxib's withdrawal focused attention on the limited capacity of drug regulatory agencies to protect public health. This was reinforced by several hasty marketing authorisations, feeble pharmacovigilance measures, and the failure to take the importance of safe drug packaging into account. No relationship could be seen between price and added therapeutic value. Vigilance is required to ensure that transparency aspects of the new European regulation are fully implemented.

The French edition of this bulletin, *la revue Prescrire* publishes a yearly review of new developments in patient management (diagnosis, prevention, drug and non drug treatments, etc.) (for 2004, see *Rev Prescrire* 257). The February issue includes a review of changes in the French pharmaceutical market.

A similar number of new drugs were examined in the "New Products" column of *la revue Prescrire* in 2004 as in previous years. Of the 685 articles on drugs published in 2004, 235 dealt with new preparations; 56 discussed noteworthy changes to drug licensing (including 25 new indications); 119 covered line extensions (formulations, dosages or presentations); 39 described miscellaneous changes or new drug names; and 234 dealt with market withdrawals (5 for safety reasons) (a).

178 of the 235 new drugs were copies, as were 52 of the 119 line extensions.

Both the number of new drugs marketed in France and the number of withdrawals from the market have tended to stabilise in recent years.

### Fewer products offering real therapeutic advance

Despite this apparent stability, 2004 differed markedly from 2003 in terms of therapeutic advance. Only six new drugs or new indications analysed in 2004 brought patients any tangible therapeutic advance, and the few real advances identified in 2004 were less decisive than those seen in 2003.

Thus, in 2003, we found that four drugs represented "a real advance" (see our in-house scoring system (b)) and that another five "offered an advantage". In contrast, none of the products assessed in 2004 was considered "a real advance", while six drugs "offered an advantage". In 2004 only a dozen new drugs or indications were considered "possibly helpful", offering a slight advantage in efficacy, safety or convenience.

For the other 200 to 400 new drugs assessed in 2004 (depending on whether or not copies and line extensions are included), the balance of benefits versus harm was similar to that of existing drugs. No clear evidence existed of a tangible clinical advantage for patients.

Seven new drugs examined in 2004 were considered "not acceptable" (the same number as in 2003) because the degree of potential benefit failed to outweigh potential harm. Thus, in our opinion, these seven drugs should not be prescribed or used.

We were unable to reach a firm opinion on four drugs in 2004 (six in 2003), as we found the evidence inconclusive; we will re-evaluate these drugs if important new data are released.

In short, despite a relatively constant number of new drugs introduced onto the market, there was less evidence of therapeutic advance in 2004 than in previous years. And health care professionals and patients are increasingly

hard-pressed to sort the wheat of therapeutic advance from the chaff of increasingly brazen promotional campaigns.

**The most aggressively promoted drugs are the least beneficial for patients.** According to our sales reps monitoring network (see the March 2005 issue of *la Revue Prescrire*, for a review of results in 2004), and on the basis of promotional material that French health care professionals received via various media, the biggest advertising campaigns in 2004 were for new drugs that were rated "nothing new".

This was notably the case for the cholesterol-lowering drugs rosuvastatin and ezetimibe; the antihypertensive drugs manidipine and olmesartan; drug combinations approved for chronic obstructive pulmonary disease (COPD), namely budesonide + formoterol and fluticasone + salmeterol; the Cox-2 inhibitors parecoxib and valdecoxib (eventually not marketed in France); and the psychotropics escitalopram and injectable olanzapine.

Major advertising campaigns were also launched for nonprescription drugs such as cetirizine and metopimazine that provide no tangible advantages.

The drugs that provided significant therapeutic advance in 2004 tended to be launched onto the market more discreetly. They include two line extensions, morphine syrup (*Rev Prescrire* 253) and paediatric tablets of atovaquone + proguanil (*Rev Prescrire* 255). These line extensions facilitate the administration of particularly useful treatments.

The six new drugs or indications that represented significant advances in 2004 affected limited groups of patients: bosentan (this issue p. 47) for patients with pulmonary arterial hypertension; enfuvirtide (this issue p. 60) for HIV-infected patients with no other alterna-

tive; laronidase (Prescrire Int 74) for some patients with type I mucopolysaccharidosis; stiripentol (this issue p. 57) for infants with severe myoclonic epilepsy; topiramate (Prescrire Int 73) as monotherapy for some patients with refractory epilepsy; and misoprostol (Rev Prescrire 253) for women seeking to terminate a pregnancy.

As in previous years, the size of an advertising campaign had nothing whatsoever to do with a drug's real therapeutic advantages.

### **Virtually uncontrolled advertising, but a growing "Just Say No" campaign**

The website of the French drug regulatory agency (<http://afssaps.sante.fr>) mentions the existence of a committee responsible for regulating drug advertising. This 31-member committee is responsible for providing recommendations on prohibitions and corrections of advertisements targeting health care professionals and for pre-screening of advertisements targeting the general public. However, it is impossible to know exactly what this committee actually does, since the website provides no timetables, minutes of meetings, opinions given, nor measures taken to avoid conflicts of interest at each meeting. Just a few general statistics were published in the annual report of the Agency's activities in 2003.

Only advertising prohibitions are published in the French *Journal Officiel*, and even these are not mentioned on the drug regulatory agency's website. We report all such bans in *la Revue Prescrire*. The accompanying rationale is always highly illustrative of the gulf between clinical evaluation and advertising spiel. In 2004 we only identified and reported 19 banned ads. This was more than in 2003 but was still only a drop in the advertising ocean.

Does this trend imply that the authorities are becoming more lax, or that advertisers are finding new ways to circumvent the rules? Whatever the case, implementation of the few published bans was slow, and their discreet publication is hardly designed to increase awareness of rogue advertising practices. Marketing campaigns often begin well before a product is launched onto the market and are well underway by the time an advertising campaign is found to be illegal.

In June 2004 the committee published recommendations on the use of

the French pharmacoeconomic agency's ratings [this agency carries evaluation of medical benefits of new drugs] in advertisements, taking this opportunity to emphasise that sales reps are required by law to provide these ratings to prescribers whenever they promote a drug (see also page 75). This is a particularly timely reminder: our sales reps monitoring network reported that only about 5% of reps voluntarily provided these ratings during promotional visits in 2004.

While conventional advertising was subject to minimal controls in France, other means of influencing health care professionals and the public were used in totally unbridled manner; these included articles in the lay media; public-private partnerships; sponsorship of scientific organisations and patients' associations; risk awareness campaigns, alerting the public to the existence of a disease or symptom; and drug company participation at public shows and exhibitions.

These worrisome practices are eliciting an increasing number of reactions from our subscribers, both individually and within organised networks that are based on the concept of "Non, merci..." ("Just Say No..."). These networks are placing a growing emphasis on independent information sources. This is an encouraging sign of growing grass-roots resistance.

### **Preventing adverse effects: improvements needed**

In 2004 French public awareness of adverse effects of medicines was heightened by the Vioxx scandal, following the worldwide withdrawal of rofecoxib by Merck Sharp & Dohme because of cardiovascular adverse effects. This event raised pointed questions to an even greater degree than did the worldwide ban of cerivastatin in 2001.

All active drugs cause adverse effects. Major efforts are therefore needed to better inform health care professionals and patients of how to minimize harmful drug effects. The individual balance of benefits versus harm must be taken into account before prescribing or using any drug. Questions inevitably arise as to whether the evaluation process currently required to obtain marketing authorisation is really adequate, whether regulatory agencies fulfil their role as a "safety barrier", and what

exactly these agencies do before and after authorising a particular drug for use by the public.

**Imprudent and ill-advised marketing authorisations.** In 2004 the French and European drug regulatory agencies approved seven drugs that, in our opinion, had a clearly negative balance of benefits versus harm (products we rated as "not acceptable") on the basis of initial evidence from clinical trials.

Thus, the inadequately assessed fixed-dose combination of levodopa + carbidopa + entacapone (this issue p. 51) increases the risk of adverse effects such as dyskinesias. Melagatran and ximelagatran (Rev Prescrire 256) are no more beneficial than existing anticoagulants but are associated with the same risks of bleeding and also possible hepatic and cardiac

adverse effects. Pimecrolimus (Prescrire Int 74), like top-

►► [see page 71]



**a-** These five market withdrawals included three products that were discontinued as a result of measures taken long ago, namely Natisedine<sup>®</sup>, a sedative combination still containing phenobarbital; Melleril<sup>®</sup> 10 mg, a thioridazine-based neuroleptic in a dose form intended for children; and Cognex<sup>®</sup>, an anticholinesterase based on tacrine, which had not been prescribed to new patients since June 2000. The other two products withdrawn for safety reasons in 2004 were Urosiphon<sup>®</sup>, a plant-based slimming aid whose excipients included a glycol ether causing renal failure (like Pilocosuryl<sup>®</sup>, which was withdrawn from the French market in 2003), and Vioxx<sup>®</sup> (rofecoxib), withdrawn worldwide because of its cardiovascular effects.

**b-** Prescrire's global assessment of new drugs and indications, represented by the Prescrire gnome named "Gaspard Bonhomme", focuses on tangible therapeutic advance offered by a given drug in a given indication. This rating system reflects not only the absolute value of the drug, based on its balance of benefits versus harm, but also its value relative to existing treatments (see page 50 for a definition of the seven score levels).

## Transparency of medicines agencies: new rules, to be applied without delay

The new European legislative framework for human medicines (Directive 2004/27/EC, currently being incorporated into national law; and Regulation (EC) 726/2004, already partly applied) imposes new obligations on drug regulatory agencies (European and national) regarding public access to official documents.

**Timetables.** Here is a list of requirements directly affecting the French drug regulatory agency.

– **French drug regulatory agency:** from 30 October 2005, Directive 2004/27/EC must be applied, and especially article 126 b: *"Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions"* (1).

– **European Medicines Evaluation Agency (EMA):** from 20 November 2004, the management board was required to implement Regulation (EC) 726/2004, and especially article 73, which refers to European regulation on public access to documents, stipulating that: *"Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents shall apply to documents held by the Agency. The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 to make available all documents that are publicly accessible pursuant to this Regulation. (...) Decisions taken by the Agency pursuant to Article 8 of Regulation (EC) No 1049/2001 may give rise to the lodging of a complaint with the Ombudsman or form the subject of an action before the Court of Justice, under the conditions laid down in Articles 195 and 230 of the Treaty respectively."* (2).

Up to 2003, the European and French drug regulatory agencies largely ignored their responsibility to provide information to health care professionals, patients, and the general public. What, if anything, changed in 2004?

**French agency: little real change.** The volume of documents made available through the French agency website (<http://afssaps.sante.fr>) has gradually increased, but these documents are of variable relevance, and much essential therapeutic information is still lacking.

Thus, the list of authorised drugs now includes 1724 of the 15 691 products concerned, but their summary of product characteristics (SPC) and patient leaflet are not always available. This is an improvement over 2003 (only 1000 drugs), but much remains to be done.

There is still no online timetable of committee meetings (relating to marketing authorisation, pharmacovigilance, etc.), nor minutes of past meetings.

On 20 December 2004, nine assessment reports on recently approved drugs were available online. Each was only a few pages long, but this was nonetheless a step in the right direction, suggesting that the agency may at least have started to comply with this regulation, explicitly required by the French Public Health Code for many years.

**Very little information on adverse effects.** In 2004 the French agency website carried a dozen letters to prescribers and ten information updates on drugs or drug classes. These documents are always brief and never include supporting data.

It is impossible for health professionals and patients to understand the reasons for and the timing of Agency decisions. Transposition of Directive 2004/27/EC into French law will, in principle, come into effect on 30 October 2005. Things should then start to change.

This lack of visibility is particularly worrisome when it comes to postmarketing surveillance of drugs with potential long-term adverse effects. Many marketing authorisations are now granted "on condition" that the company conducts further long-term clinical trials, pharmacovigilance studies of the first patients to be treated, or other types of studies. No information is currently released on whether these studies are actually done or on any practical implications of their results. For the first time, in December 2004, the Agency published a small list of drugs being actively followed up; the list was then modified, with no explanation whatsoever.

Another pretext for withholding information is that the French agency is "awaiting results of ongoing work at the European agency". Thus, the benefits of European-level expert opinions are offset by information retention for several months at the national level. What is there to prevent the French agency, pending a European review, from publishing a review of French data online? This would be a simple and constructive way of encouraging the work of European experts and of keeping patients and caregivers informed.

**EMA: very little progress.** Neither the number nor the quality of documents available on the EMA website increased in 2004. The SPCs and assessment reports (EPARs) published on the EMA website (<http://www.emea.eu.int>) are presented in a way that makes it very difficult to detect changes from one version to another. Thus, important information relating to the indications, dose regimen, warnings or precautions are barely identifiable, even to the practised eye. Some small improvements were made to EPARs in 2004, such as the addition of reference lists distinguishing between published and unpublished clinical trials.

**Towards an end to mutism and euphemism.** Otherwise, EMA remains as secretive as ever, with no full reports of committee or task force meetings, no precise rationale for decisions (including publication of minority opinions and, if need be, voting details), and exceedingly rare pharmacovigilance data.

Texts placed online are always very short and understated, even when they deal with adverse effects. This was notably the case of communiqués published in 2004 on the risks of selective serotonin reuptake inhibitor antidepressants in adolescents and on Cox-2 inhibitors. As to the Cox-2 inhibitors, in April 2004 EMA stated *"it can be considered that there may be a small safety disadvantage of COX-2 inhibitors compared to conventional NSAIDs (Prescrire Int 74)"*. A fine euphemism indeed! Let's hope that the results of EMA's re-assessment of Cox-2 inhibitors will be more informative.

EMA has much to do in terms of transparency and public information if it is to comply with new Regulation (EC) 726/2004. The European agency will be able to count on *Prescrire* and the Medicines in Europe Forum, among others, to remind it of its new obligations. We will not hesitate to use every means possible to eradicate secrecy in one of the key European health institutions.

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1- "Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use: 30 April 2004 L136/34-L136/57".

2- "Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency: 30 April 2004 L136/1-L136/33".

24 years of *Prescrire* ratings for new drugs (a)

Rating (b)	Number	%
<b>Bravo</b>	7	0.23
<b>A real advance</b>	77	2.49
<b>Offers an advantage</b>	223	7.20
<b>Possibly helpful</b>	467	15.08
<b>Nothing new</b>	2 109	68.12
<b>Not acceptable</b>	87	2.81
<b>Judgement reserved</b>	126	4.07
<b>Total</b>	3 096 (c)	100

a- 1981 through 2004.

b- See this issue, page 50, for a detailed description of the *Prescrire* rating system.

c- This number corresponds to new preparations (or indications)

marketed to community and hospital physicians, and which were rated by *Prescrire*. It does not include over-the-counter products or range extensions (new dose strengths, formulations, etc.).

► ical tacrolimus (*Prescrire* Int 71), is no more effective for atopic eczema than topical steroids, whereas the potential long-term adverse effects of this immunosuppressant, especially in children, are unknown. It is also unclear whether injectable risperidone is at least equivalent to injectable neuroleptics for schizophrenic patients, in terms of the balance of benefits versus harm (*Rev Prescrire* 255). This drug is less convenient to administer. Nasal sumatriptan (this issue p. 45) was approved for use in adolescents with migraine, yet its analgesic effect is uncertain and at best modest. Only placebo comparisons are available. Nasal sumatriptan has not been proven effective in reducing nausea or photophobia, and it carries a risk of cardiovascular adverse effects. Thalidomide (*Prescrire* Int 72), a useful drug in other indications, has no proven benefit in chronic graft-versus-host disease (a new indication) but has many adverse effects.

This alarming list, drawn up in the course of a single year, demonstrates that the French and European drug regulatory agencies are not adequately protecting the public.

**A few common-sense pharmacovigilance measures.** In 2004 the French agency took a number of welcome measures aimed at limiting the dangers associated with particular drugs already on the market. These measures often consisted of changes in regulatory status or modifications to the summary of product characteristics (SPC), sometimes accompanied by a warning to prescribers.

In 2004 we reported the following measures (among others) in *la Revue Prescrire* (listed in order of publication):

- a ban on all products based on ephedrine (used for weight loss), because of a risk of adverse effects (especially cardiovascular and hepatic);
- classification of dipotassium clozapate 50 mg as “narcotic-like” (special prescription forms, and prescription for less than 28 days), because of the risk of dependence;
- modification of the SPCs for some products containing pseudoephedrine, following a re-evaluation of this vasoconstrictor, which is associated with numerous adverse effects;
- modification of the SPC and patient leaflet for olanzapine because of a risk of stroke and death in elderly patients with dementia;
- modification of the SPC for rosuvastatin because of a risk of rhabdomyolysis, observed at all doses;

- modification of the SPC for Nisapulvol<sup>®</sup> powder (talc + benzyl parahydroxybenzoate), because of cutaneous reactions in children with chickenpox;
- withdrawal of Pilosuryl<sup>®</sup> oral solution in 2003 and Urosiphon<sup>®</sup> in 2004, because of cases of renal failure and neurological disorders linked to a glycol ether excipient authorised some years previously (Pilosuryl<sup>®</sup> was recently reintroduced to the market, without the glycol ether excipient);

- classification of amineptine as a narcotic, 26 years after the first reports of dependence for this antidepressant, which was withdrawn from the French market in 1999. However, tianeptine, which is chemically related to amineptine and has also been linked to cases of dependence, is still on the market and is not registered as a narcotic.

The French agency released information and recommendations (always extremely brief) on adverse effects through a variety of channels:

- in January 2004 an opinion from the pharmacoeconomic Committee contained data on the haematological adverse effects of linezolid; the Committee had first raised doubts as to the safety of this product in 2001;
- an update on the risk of tuberculosis linked to infliximab, an immunosuppressant used in rheumatology and gastroenterology, was placed online with recommendations for patient monitoring;
- a press release in December 2004 emphasized the lack of proven efficacy of selective serotonin reuptake inhibitor antidepressants in children, and the risk of increased suicidal behaviour in children treated with these drugs (a risk established more than 18 months previously...);
- an update on the safety of Cox-2 inhibitors was released in July 2004,

concluding that the balance of benefits versus harm remained favourable.

- a press release in December 2004 announced the suspension of a clinical trial of celecoxib for the treatment of colonic polypsis;

- an update was released in December 2004 on the use of mitoxantrone in multiple sclerosis, warning of a risk of induced leukaemia.

**Dangerously lax.** Some measures taken in 2004 as well other awaited measures not yet taken, are not likely to reduce the risks of adverse effects.

Thus, pioglitazone and rosiglitazone had been classified initially as “drugs of exception”, for which prescribing should be restricted. The removal of this status will inevitably lead to an increased use of these oral antidiabetics. Yet the risk of potentially serious adverse effects (water-sodium retention, heart failure) and uncertainties regarding long-term benefits call for special caution, particularly in view of the way these products have been aggressively promoted to physicians.

Switching metopimazine (a neuroleptic) from prescription-only to over-the-counter drugs status in adults and the extension of its rectal indications in infants are likely to increase the risk of unnecessary use.

The increased number of tablets in boxes of all 5HT<sub>1</sub> receptor agonists (triptans) used to treat migraine attacks and the virtual disappearance of smaller boxes, are also likely to contribute to increased consumption, increasing the risk of drug-induced headache and cardiovascular adverse effects.

Following an earlier ban, the French government approved the marketing of flavoured and chewable high dose ►►

► aspirin products, even though such products have been linked to life-threatening accidental overdose in small children.

**The French government pass the buck to EMEA.** Finally, it appears that measures affecting drug classes associated with major risks (Cox-2 inhibitors and antidepressants for example) are often slow in coming in France. The French drug regulatory agency explains these delays by citing work "underway" at EMEA. Because communiqués dealing with established dangers are always brief and often published late, precise pharmacovigilance information trickles down very slowly to health professionals and patients (see page 70).

### Reimbursement? No problem!

Without going into the details of drug price determinants, the real costs of research, and the lack of effective controls in France, there were some noteworthy events in 2004.

**High prices bearing no relation to added therapeutic value.** Although France, like many other EU member states, claims to "negotiate" the prices they set for new products, these prices remain inexplicably high and bear little if any relation to the degree of therapeutic advance. For example, 28 tablets of methylphenidate 36 mg cost 56.48 euros, and 28 doses of teriparatide cost 398.87 euros.

Yet the drug pricing authorities are capable of standing up to drug companies when they choose to do so: this was apparently the case for valdecoxib, which Pfizer eventually decided not to market in France (Rev Prescrire-251) (c).

Prices are rarely revised downwards when the indications for a given drug are extended. The most striking example at present is that the price of Cox 2 inhibitors remains virtually unchanged, even though it is finally dawning on EU drug regulatory agencies that these drugs offer no tangible advantages over conventional NSAIDs and have higher risks of serious adverse effects. The prices of selective serotonin reuptake inhibitor antidepressants have not fallen substantially in France even though their indications have been markedly extended; likewise for sumatriptan. Most significant price cuts affect drugs with already inflated prices: one example is the 20% cut in the price of

### The 27 new drugs or indications approved through the European centralised procedure and examined in *La revue Prescrire* in 2004

Rating (a)	Number	INN and trade names
<b>Bravo</b>	0	–
<b>A real advance</b>	0	–
<b>Offers an advantage</b>	3	bosentan (Tracleer°), enfuvirtide (Fuzeon°), laronidase (Aldurazyme°)
<b>Possibly helpful</b>	7	atazanavir (Reyataz°), infliximab (Remicade°) (b,c), mycophenolate mofetil (Cellcept°) (d), palivizumab (Synagis°) (e), pegvisomant (Somavert°), arsenic trioxide (Trisenox°)
<b>Nothing new</b>	16	adalimumab (Humira°), aprepitant (Emend°), bimatoprost (Lumigan°), caspofungin (Cancidas°) (f), docetaxel (Taxotere°) (g), entacapone (Comtan°) (h), emtricitabine (Emtriva°), ethinylestradiol + norelgestromin (Evra°), insulin aspart (NovoRapid° - NovoMix° 30), olanzapine (Zyprexa°) (i), olopatadine (Opatanol°), parecoxib (Dynastat°), tenofovir (Viread°) (j), teriparatide (Forsteo°), valdecoxib (Bextra°) (k)
<b>Not acceptable</b>	1	levodopa + carbidopa + entacapone (Stalevo°)
<b>Judgement reserved</b>	0	–

a- See our ratings page 50.

b- In ankylosing spondylarthritis.

c- In Crohn's disease, long-term.

d- In renal transplantation in children.

e- For preventing SRV infections in children less than 2 years having congenital heart disease.

f- For invasive candidiasis.

g- First-line, non small-cell lung cancer.

h- Parkinson's disease, second look.

i- For agitation, and for the injectable form only.

j- HIV infection, first-line.

k- Eventually not marketed in France in 2004.

Rebif° 44 µg (interferon beta-1a), bringing the cost of a box of 12 pre-filled syringes down from 1165.85 to 968.15 euros.

Catalogue prices of new drugs also remain high in the hospital setting, even when the indications are extended. Thus, gefitinib and adalimumab are to be sold at respectively 1950 euros for 30 tablets and 1300 euros for two syringes. The prices of older drugs with increasingly numerous indications, such as docetaxel, have hardly changed over the years (737.85 euros per bottle of 80 mg). These prices are theoretically negotiable by individual hospitals, but if such negotiation indeed take place their results are not publicly available.

### Some basic drugs are too cheap.

On the other hand, prices of some older drugs remain low, sometimes too low. Low prices for older drugs are one reason why companies only promote costlier new drugs or withdraw useful but unprofitable older drugs. 2003 saw the demise of chlortalidone, desipramine, nedocromil, and sodium cromoglycate. The price of hydrochlorothiazide has remained very low in France, yet this is recommended as a first-choice antihypertensive.

The price of isoniazide was multiplied by a factor of 9.5 in 2004 in order to persuade the manufacturer to keep this antituberculous drug on the market. Similar measures could no doubt prevent other regrettable drug withdrawals: for example, there is only one prepa-

ration of injectable hydrocortisone and one preparation of penicillin V available in France.

### Copies: more than a cost saving, an opportunity to promote the INN

The French generics policy masquerade continued in 2004.

After asserting for decades, with no legal basis whatsoever, that prescriptions written in international non proprietary names (INN) were forbidden, the French government finally permitted INN-based prescribing in 2002. After granting pharmacists the right to dispense a generic instead of a trade-name product written on a prescription, the government created a number of obstacles. By publishing a complex generics list, then a "fixed tariff" to which most originator manufacturers adhered, they strongly discouraged the use of generics and copies in general (Prescrire Int 73).

Nothing really changed in 2004. Paracetamol, an old, widely used and highly useful drug is still not included in the generics list, and the French drug regulatory agency has offered no expla-

c- Valdecoxib, which was never marketed in France, offered no therapeutic advantage; there is now evidence of cardiovascular and cutaneous adverse effects (this issue p. 63). Was Pfizer's commercial turn-around linked to these adverse effects?

nation for this omission. Companies that market originator drugs do their best to delay the arrival of copies, often by promoting isomers or metabolites of their originator products. Note that INN prescribing, which avoids many regulatory pitfalls, is not facilitated by the most popular prescription software programmes.

**Fewer useless drugs copied in 2004.** In terms of therapeutic value, 26.5% of copies assessed in *la Revue Prescrire* in 2004 contained a substance with a positive balance of benefits versus harm and clearly demonstrated therapeutic value. In contrast, 9% contained a substance with only placebo value, and 3.5% a substance that is best avoided. The remaining 61% of copies contained substances with proven efficacy but little relative value, or substances that had been less well assessed than treatment alternatives.

Most copies that now appear on the market include the INN alongside their trade name, which can contribute to patient information provided that the INN appears in larger type than the trade name. However, generics are still launched onto the market with fantasy names, especially when intended for pharmacist counselling or self-medication. In addition, the same commercial name sometimes covers an entire “umbrella range” of drugs with different compositions.

These trends illustrate the value of using the INN when discussing treatment options or dispensing medications, and of showing patients how to recognise the INN on the drug packaging.

## The tide is turning

Our review of the year 2000 ended with the following statement: “*a drug market overwhelmed by a plethora of offers, a market less and less bothered by medicines agencies, who are becoming increasingly sympathetic to industry's interests and little to show, in terms of public health, for the growing drug bill*” (Prescrire International 52).

The situation in 2004 was very similar, but with one major difference: the major pharmaceutical companies, having focused for too long on profitable markets ensuring short-term profits for their shareholders, are now finding that their product pipeline is drying up. The drugs they are now launching, usually for conditions for which we already have adequate treatments, provide

## The 23 new drugs or indications approved through the European mutual recognition procedure and examined in *La revue Prescrire* in 2004

Rating (a)	Number	INN and trade names	Rapporteur country (b)
Bravo	0	–	–
A real advance	0	–	–
Offers an advantage	0	–	–
Possibly helpful	3	anastrozole (Arimidex°) (c) topical diclofenac 3 % (Solaraze°) valganciclovir (Rovalcyte°) (d)	United Kingdom United Kingdom The Netherlands
Nothing new	16	aceclofenac (Cartrex°) budesonide + formoterol (Symbicort°) (e) dutasteride (Avodart°) escitalopram (Seroplex°) estradiol + dienogest (Climodiene°) ezetimibe (Ezetrol°) fludarabine intravenous (Fludara°) (f) fluticasone + salmeterol (Seretide° Diskus°) (e) fluvoxamine (Floxyfral°) (h) ketotifen eye drops (Zaditen°) manipidine (Iperfen°) olmesartan medoxomil (Alteis° - Olmetec°) rosuvastatin (Crestor°) influenza vaccine with squalene adjuvant (Gripguard°) meningococcal C vaccine conjugated with tetanus toxoid (Neisvac°)	Sweden Sweden Sweden Sweden The Netherlands Germany United Kingdom (g) (i) Sweden Italy Germany The Netherlands Germany United Kingdom
Not acceptable	1	pimecrolimus (Elidel°)	Denmark
Judgement reserved	3	alteplase (Actilyse°) (j) botulinum type A toxin (Botox° - Dysport°) (k)	Germany Ireland

a- See our ratings page 50.

b- Excluding cases where France was rapporteur.

c- In adjuvant treatment of non metastatic breast cancer.

d- In prevention of CMV infection following solid organ transplantation.

e- In chronic obstructive pulmonary disease.

f- In chronic lymphoid leukaemia, first-line.

g- Through the EU arbitration process.

h- In obsessive-compulsive disorder.

i- EU harmonisation process.

j- In ischaemic stroke.

k- In upper limb spasticity after stroke.

patients with practically no therapeutic advantage whatsoever.

Instead of reorienting their research and development towards unmet needs, notably for diseases affecting poor countries, the major pharmaceutical companies have lost sight of their true vocation in recent years, under the benign eye of so-called “regulatory” agencies. Too many companies are now engaged in pseudo-innovation, inventing new needs, forcing hasty marketing approval of inadequately evaluated new drugs, and exposing those who use their drugs to increasing dangers. Drug regulatory agencies, being funded principally by the companies they serve, are standing by passively, while attempting to cover their backs by engaging in intense administrative agitation and keeping silent about the real issues. Meanwhile, French health care services continue to cough up the money for new, expensive drugs, at least for now.

The consequences are already being keenly felt. There are a growing number of pharmacovigilance scandals, not only because new drugs can have seri-

ous adverse effects, but also because many drugs intended for widespread use offer no clear advantages yet expose large numbers of patients to unjustified risks.

The public is starting to realise that something is wrong; the media is beginning to accuse “opinion leaders” of being nothing more or less than “disinformation dealers”; patients are starting to wonder exactly why profit-making companies should sponsor patient groups; and health care service providers are consulting with their counterparts in other countries in an attempt to find a solution to massive price increases.

Change will come, but it will be neither rapid nor radical: multinational pharmaceutical companies, drug regulatory agencies and health service providers are like ocean liners: they continue to float despite gaping holes in their substructure and are painfully slow to change course. But gradual change towards more rational use of medicinal products will inevitably come.

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