

Adapted from *Rev Prescrire* February 2006; 26 (269): 140-150

A look back at the pharmaceuticals market 2005

Deregulation continues

- **Market approval is often granted despite inadequate evaluation of the drug or indication concerned.**
- **Pharmacovigilance policies remain overcautious and biased in favour of drug companies.**
- **New EU requirements for transparency of regulatory agencies were not adopted in France in 2005.**
- **The prices granted for new drugs still bear little relation to R&D costs or to therapeutic advantages.**
- **By seeking to sustain a pharmaceutical industry that is no longer innovative, governments are neglecting their mission to protect public health.**

In this article, as we do every year at this time, we take a look back at trends in the French pharmaceuticals market, based on the results of our evaluations in 2005.

Mainly bogus innovation

We examined 600 drug files in 2005, compared with 685 in 2004. The difference mainly reflects the smaller number of market withdrawals in 2005.

These 600 files break down as follows: 231 new products (or product ranges), i.e. 231 new brand names (a) (more than three-quarters of which were simple copies); 124 line extensions (new dose strengths, new formulations, etc.); 52 noteworthy changes in marketing conditions (about half involving new or extended indications); 37 changes in brand name or composition (a new drug replacing an existing product), and two products that we re-examined as more data became available with longer follow-up. We also reported on 154 effective marketing withdrawals, including 11 for safety reasons (5 of which belonged to the same family of "immunostimulants").

Very few new drugs. Excluding copies, we examined only about 50 new products in 2005. Some were combinations of existing drugs, and others new modes of administration of existing drugs or re-introductions of old drugs that had been taken off the market.

Some of the new drugs examined in 2005 were simple derivatives of existing drugs: for example, fosamprenavir is a simple metabolic precursor of amprenavir; mycophenolate sodium is a salt, while mycophenolate mofetil is an ester; levobupivacaine is a simple isomer of bupivacaine.

Thus, about 30 pharmacologically and chemically new drugs were introduced onto the French market in 2005. The therapeutic value of these products was highly uneven.

Only 40% of copies concerned truly valuable drugs. Among the 178 copies examined in *la revue Prescrire* in 2005, about 40% involved drugs with well-documented risk-benefit ratios and proven therapeutic value. Five of these products had previously been protected in France by patents or complementary protection certificates, and were being copied for the first time; they were (in alphabetical order): alendronic acid, ciprofloxacin, fluconazole, lisinopril, and simvastatin.

In contrast, 7% of copies examined in 2005 involved active ingredients or combinations that are best avoided, such as ciprofibrate; a dextropropoxyphene + paracetamol + caffeine combination; rilmenidine.

Marketing authorisation: virtually a free-for-all

To an even greater extent than in 2004, 2005 saw the market release of very few new drugs offering real therapeutic advantage: we only rated 1 product "A real advance", and only 4 others "Offered an advantage".

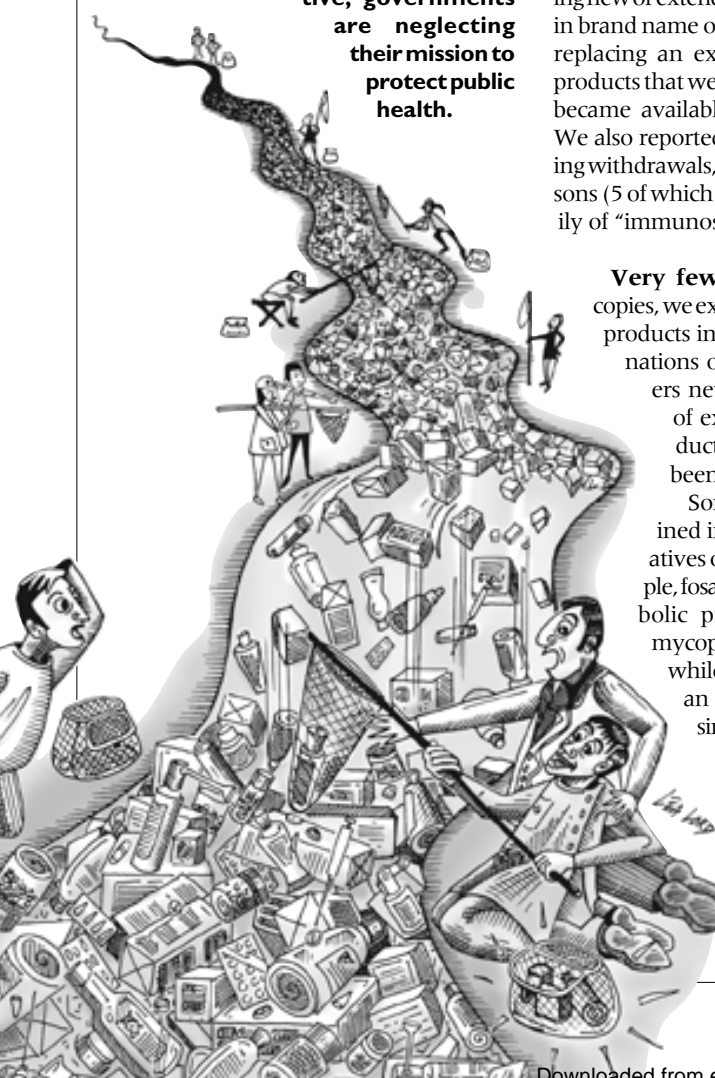
These products were singled out in the 2005 *Prescrire* New Drug Awards (see this issue p. 72).

Twenty new drugs or indications approved in 2005 offered an advantage in terms of efficacy, safety or convenience, and were considered "Possibly helpful".

We reserved judgement on 2 new products because the available clinical data failed to show their precise therapeutic value; these files will be re-opened at a later date, when and if significant new data become available.

An increase in poorly assessed "innovations" carrying unjustified risks. 2005 also saw an increase in the number of new products that we found to be "Not ▶▶

a- *Prescrire's* global assessment of new drugs and indications, represented by the *Prescrire* gnome named "Gaspard Bonhomme", focuses on tangible therapeutic advances offered by a drug for a specific indication. This rating system reflects not only the absolute therapeutic value of the drug, based on its risk-benefit ratio, but also its value as compared to existing treatments (see page 42 for a definition of the seven score levels).



2005 TRENDS

New drugs approved through the European centralised procedure and examined in *La revue Prescrire* in 2005

Rating (a)	Number	INN and trade names
Bravo	0	–
A real advance	0	–
Offers an advantage	2	<i>pemetrexed</i> (Alimta [®]) (b), <i>zinc</i> (Wilzin [®])
Possibly helpful	5	<i>bortezomib</i> (Velcade [®]), <i>fulvestrant</i> (Faslodex [®]), <i>insulin glargine</i> (Lantus [®]), <i>miglustat</i> (Zavesca [®]), <i>pregabalin</i> (Lyrica [®]) (c)
Nothing new	10	<i>abacavir + lamivudine</i> (Kivexa [®]), <i>aripiprazole</i> (Abilify [®]), <i>bivalirudine</i> (Angiox [®]), <i>liposomal cytarabine</i> (Depocyte [®]), <i>fosamprenavir</i> (Telzir [®]), <i>pemetrexed</i> (Alimta [®]) (d), <i>pramipexole</i> (Sifrol [®]), <i>pregabalin</i> (Lyrica [®]) (e), <i>ranelate strontium</i> (Protelos [®]), <i>vaccine against cholera</i> (Dukoral [®])
Not acceptable	8	<i>celecoxib</i> (Onsenal [®]) (f), <i>cetuximab</i> (Erbix [®]), <i>duloxetine</i> (Yentreve [®]) (f), <i>efalizumab</i> (Raptiva [®]), <i>ibritumomab</i> (Zevalin [®]), <i>rosiglitazone + metformin</i> (Avandamet [®]), <i>tasonermin</i> (Beromon [®]), <i>tolcapone</i> (Tasmar [®])
Judgement reserved	1	<i>porfimer</i> (PhotoBarr [®])
Total	26	

a- See our ratings page 42.

b- Non resectable pleural mesothelioma.

c- Neuropathic pain.

d- Non small-cell lung cancer.

e- Combination therapy, epilepsy.

f- Not marketed as of December 2005.

acceptable", because available clinical data showed that the risks outweighed the potential benefits. Nineteen new products were considered "Not acceptable", including 7 new drugs, 9 new indications, and 3 line extensions. *Prescrire* analysed 2 of these products before they were released onto the French market.

The new drugs in question have serious adverse effects but no proven therapeutic advantage over existing products. Some examples include:

- efalizumab (*Prescrire Int* 81), in plaque psoriasis: risk of skin cancer and potentially severe infections;

- cetuximab (*Prescrire Int* 80), in colorectal cancer: risk of acne and hypersensitivity reactions;

- radiolabeled ibritumomab (*Prescrire Int* 80), in some forms of non Hodgkin's lymphoma: complicates treatment and has disappointing efficacy and tolerability;

- celecoxib (*Prescrire Int* 80) was assessed for only 6 months, at a dose of 800 mg/day, in colorectal cancer prevention in patients with familial adenomatous polyposis;

- duloxetine (*Prescrire Int* 80), in stress urinary incontinence: adverse effects include dizziness, nausea, hepatic disorders, suicide attempts, etc.;

- tasonermin (*La revue Prescrire* 267): only fragmentary evidence of efficacy in soft-tissue sarcomas, but potentially serious and poorly documented adverse effects;

- dactinomycin (*La revue Prescrire* 263): this antibiotic, long used as a cytotoxic agent, is associated with haematological, gastrointestinal and hepatic adverse effects in most patients;

- tolcapone (this issue p.54) is back on the market in France for Parkinson's disease (albeit with certain restrictions), even though it had been withdrawn in 1998 because of fatal hepatitis.

Assessment elsewhere. Some people find *Prescrire's* judgements particularly severe, perhaps because they are more used to drug companies' and so-called opinion leaders' propaganda. Yet our opinions are in no way atypical. See, for example, the comparison of our conclusions with the French Transparency committee's "medical benefit scores" in 2004 (*Prescrire Int* 76). In addition, in 2005 we reported the results of a comparison between *Prescrire's* scores and the judgements of the Swedish regulatory agency, which were in agreement in 74% of cases and showed no major disagreement (*Prescrire Int* 80).

Easy marketing authorisation, whatever the procedure. Compared to 2004, more new drugs, new fixed-dose combinations and new indications were approved through the European centralised procedure in 2005: 39 centralised European marketing authorisations were granted by the European Commission, following the recommendations of the European Medicines Agency (EMA). In comparison, there were 15 mutual recognition procedures (authorisations first granted in one Member State) and 14 national marketing authorisations granted by the French regulatory agency.

Whatever the agency, the proportion of authorised drugs that offered real therapeutic advance was similar (see tables p. 76-77).

Thus, in 2005, regulatory agencies are no longer fulfilling their regulatory role, and are authorising drugs that expose patients to sometimes serious dangers without offering them any significant therapeutic benefits.

Risk prevention: don't rock the boat...

Welcome measures were taken in some countries and in the European Union, whereas the French government dragged its feet.

For instance, an aspirin-based combination (Alka-Seltzer[®]) was only subjected to certain restrictions in France; in contrast, the Spanish health authorities required removal of aspirin from this product, which is intensely marketed to the public and is traditionally used as a hangover cure. Another "hidden" source of aspirin reappeared on the French market in 2005 (Solucetyl[®]) (*La revue Prescrire* 268).

The Spanish regulatory agency also prohibited extemporaneous mixtures containing appetite suppressants such as benflorex, a drug derived from an amphetamine appetite suppressant that was withdrawn from the market because of serious adverse effects (pulmonary arterial hypertension and cardiac valve disease) (*La revue Prescrire* 264).

Following an arbitration procedure requested by Finland, the EMA concluded that nimesulide, an anti-inflammatory drug with serious hepatic adverse effects, had an overall positive risk-benefit ratio. The French agency simply followed suit, even though marketing of nimesulide had been suspended in Finland and Spain in 2002 (*La revue Prescrire* 228).

Veralipride, a neuroleptic marketed in France (as it was in Spain) for the treatment of hot flushes associated with menopause, was withdrawn from the Spanish market because of its adverse effects, which include parkinsonian symptoms (*La revue Prescrire* 264).

The dextropropoxyphene + paracetamol combination was withdrawn from the Swedish and British markets due to deaths from both intentional and accidental overdose (this issue p. 20). Products based on dextropropoxyphene were also withdrawn from the Swiss market in 2003. However, according to a press release issued on 28 July 2005, the French agency "did not envisage any special measures", and simply issued a reminder of the need to respect the recommended dose regimen.

A trickle of information on recent problem drugs. The Cox-2 inhibitor saga continued in 2005. The European agency took a number of half-measures, modifying the Cox-2 inhibitor SPCs, adding a contraindication in some patients and an infor-

mation update on patients with cardiovascular risk factors (*Prescrire Int* 77). The French agency simply followed suit.

Valdecoxib (not marketed in France) was withdrawn from the American market at the request of the Food and Drug Administration (FDA), and the European Commission has since suspended this product's centralised European marketing authorisation because of its negative risk-benefit ratio (*La revue Prescrire* 267). Marketing authorisation for parecoxib was suspended by the Swiss regulatory agency (*La revue Prescrire* 263), and the FDA refused to approve this Cox-2 inhibitor (*La revue Prescrire* 266).

In France, as 2005 drew to a close, we were still waiting for a public statement on the degree of harm caused by rofecoxib. Parecoxib is still marketed for use in hospitals. Celecoxib is also still available from both community and hospital pharmacies, even though it is no more effective than standard NSAIDs, does not prevent serious gastrointestinal adverse effects, and exposes patients to serious cardiovascular and cutaneous adverse effects (*Prescrire Int* 76).

Monoclonal antibodies, which were eagerly rushed onto the markets, have poorly investigated and documented adverse effects. For example, infliximab was linked to cases of severe hepatitis and to an increased risk of lymphoma (*Prescrire Int* 79). Allergic reactions, thrombocytopenia, leukopenia and infections occurred with adalimumab (*La revue Prescrire* 261). Hypersensitivity reactions during and after infusion, and hypomagnesaemia, have recently been identified as adverse effects of cetuximab, which was already known to cause skin reactions, hypersensitivity and interstitial pneumonia (*La revue Prescrire* 266). New data on the cardiotoxicity of trastuzumab support those obtained in initial clinical trials (*Prescrire Int* 81), yet the French Agency has released little information (to healthcare professionals or patients), while at the same time the approved uses of these drugs are extended.

Device surveillance. The French Agency's website now includes a section for reporting of adverse effects linked to medical devices and on follow-up of such reports, including any measures taken.

One example of active device surveillance was the enquiry into complications associated with slings used to treat stress urinary incontinence and prolapse (*La revue Prescrire* 260).

In a public statement dated 12 May 2005, the French Agency issued a reminder on radioprotection measures, following cases of exposure to doses 20% above those intended for cancer therapy.

These examples of active monitoring of

New drugs approved through the European mutual recognition procedure and examined in *La revue Prescrire* in 2005

Rating (a)	Number	INN and trade names	Rapporteur country
Bravo	0	–	–
A real advance	1	<i>chickenpox vaccine</i> (Varivax [®])	Italy
Offers an advantage	0	–	–
Possibly helpful	3	<i>eplerenone</i> (Inspra [®]) <i>ethinylestradiol + etonogestrel</i> (Nuvaring [®]) <i>tick-borne meningoencephalitis vaccine</i> (Ticovac [®] enfants)	The Netherlands The Netherlands Austria
Nothing new	11	<i>betamethasone + calcipotriol</i> (Daivobet [®]) <i>calcitriol</i> (Silkis [®]) <i>ciclopirox olamine</i> (Sebiprox [®]) <i>epinastin</i> (Purivist [®]) <i>everolimus</i> (Certican [®]) <i>levobupivacaine</i> (Chirocaïne [®]) <i>metformin + glibenclamide</i> (Glucovance [®]) <i>mycophenolate sodium</i> (Myfortic [®]) <i>neбиволол</i> (Nebiloх [®] - Temerit [®]) <i>solifenacin</i> (Vesicare [®]) <i>vaccine against typhoid + vaccine against hepatitis A</i> (Tyavax [®])	Denmark The Netherlands France Sweden Sweden Sweden France France The Netherlands The Netherlands United Kingdom
Not acceptable	0	–	
Judgement reserved	0	–	
Total	15		

a- See our ratings page 42.

New indications approved through the European centralised procedure and examined in *La revue Prescrire* in 2005 (a)

Rating (b)	Number	INN and trade names
Bravo	0	–
A real advance	0	–
Offers an advantage	1	<i>trastuzumab</i> (Herceptin [®]) in some breast cancers in combination with <i>docetaxel</i>
Possibly helpful	4	<i>docetaxel</i> (Taxotere [®]) prostatic cancer; <i>etanercept</i> (Enbrel [®]) ankylosing spondylitis; <i>imiglucerase</i> (Cerezyme [®]) type 3 Gaucher's disease; <i>paclitaxel</i> (Paxene [®]) Kaposi's sarcoma linked to AIDS
Nothing new	4	<i>ibandronic acid</i> (Bondronat [®]) prevention of complications of bone metastases in breast cancer; <i>darbepoetin alfa</i> (Aranesp [®]) anemia linked to chemotherapy of cancers; <i>etanercept</i> (Enbrel [®]) plaque psoriasis; <i>olanzapine</i> (Zyprexa [®] - Zyprexa Velotabs [®]) in prevention of relapses in bipolar disorder
Not acceptable	5	<i>leflunomide</i> (Arava [®]) in psoriatic rheumatism; <i>pioglitazone</i> (Actos [®]) single therapy of type 2 diabetes; <i>pioglitazone</i> (Actos [®]) combination therapy in type 2 diabetes; <i>rosiglitazone</i> (Avandia [®]) single therapy in type 2 diabetic patients; <i>rosiglitazone</i> (Avandia [®]) combination therapy in type 2 diabetes
Judgement reserved	1	<i>caspofungin</i> (Cancidas [®]) suspected fungal infections in adult patients with neutropenia
Total	15	

a- In 2005 there was no mutual recognition dossier for new indications presented in *la revue Prescrire*.

b- See our ratings page 42.

medical devices, albeit few in number, are encouraging signs in a very large yet loosely regulated market.

Prices: the upward spiral continues

In 2004 we wrote that drug prices have nothing to do with R&D costs and medical benefits (*Prescrire Int* 75). Nothing much changed in 2005.

Prices unrelated to therapeutic advance. The French pricing committee still grants very high prices for new drugs, regardless of therapeutic advance and, in some cases, regardless of the Transparency committee's opinion concerning the medical benefits of these new drugs.

Here are a few examples:
– the price granted to GlaxoSmithKline for fondaparinux (used prophylactically) represents a treatment cost of [go to page 79] ▶▶

Regulatory agencies pay lip service to data transparency

The new European legislative framework for human medicines, adopted in 2004, raised hopes that regulatory agencies would become more transparent. Directive 2004/27/EC and Regulation (EC) 726/2004 both call on EMEA and national agencies to fulfil clear obligations concerning public access to the documents they hold.

Several recent pharmacovigilance scandals, including the global withdrawal of rofecoxib in September 2004 drew attention to the roles and responsibilities of regulatory agencies, especially concerning transparency.

An explicit European Directive. By 10 January 2006, Directive 2004/27/EC had only just started to be integrated into French law. Only a few articles of the Directive had been transposed, primarily articles relating to generic drugs and marketing authorisation, which are mainly of interest to pharmaceutical firms.

Articles dealing with transparency and with the independence of the French national agency had still not been transposed, even though the official deadline to do so was 30 October 2005.

In particular, article 126b stipulates that: "In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry which could affect their impartiality. These persons shall make an annual dec-

laration of their financial interests. In addition, the 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".

Other articles of the Directive concern access to assessment reports held by regulatory agencies. Article 21-4 requires that "The competent authorities shall make publicly accessible without delay the assessment report [Editor's note: which forms the basis of marketing authorisations], together with the reasons for their opinion (...). The justification shall be provided separately for each indication applied for (...)". Article 102, which concerns "information obtained about adverse reactions to medicinal products", states that such information must be recorded in the Agency's database, and "shall be permanently accessible to all Member States and without delay to the public".

As of February 2006, the situation was still far from satisfactory:

- most summaries of product characteristics (SPC) and patient leaflets for drugs authorised in France are still not available on the Agency's website, despite some progress (4338 SPCs for 16 506 authorised products);
- assessment reports on drugs approved in France are still rarely published online (only 22 as of 31 December 2005) considering the number of approved drugs, and some reports are not released in a timely manner (for example 2 years after marketing authorisation of ximelagatran and melagatran);
- no agenda of meetings of the Agency's various committees and task forces is publicly available, with the exception of those pertaining to the device surveillance committee;
- no records of these meetings are made public;
- concerning pharmacovigilance, the Agency's 2004 annual report mentions 2 940 periodic safety update reports (PSURs) submitted to the French regulatory agency, 43 files submitted to the pharmacovigilance technical committee, and 18 files submitted to

Adapted from *Rev Prescrire* February 2006; 26 (269): 103

EU Directives apply directly after the transposition date has expired

In its case-law the European Court of Justice has regularly decided that European citizens who consider themselves penalized by a national law that conflicts with a Directive can invoke the provisions of the Directive. Thus, once the date limit for transposition has expired, EU Directives acquire a "direct effect", implying that all Member States are obliged to interpret and apply their national legislation accordingly (1). According to EU case-law, "the Member State is acting equivocally and unlawfully if it applies its old law without adapting it to the requirements of the directive or recommendation".

Thus, Member States' regulatory agencies and drug companies must comply with Directive 2004/27/EC, whether or not it has been transposed into national law.

Among the articles of Directive 2004/27/EC that have not yet been transposed in France, the article relating to "added therapeutic value" is particularly interesting. Article 10-1 paragraph 4 stipulates that: "The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies". It thus obliges companies to demonstrate "added therapeutic value" when applying for an extension of the data protection period. Transposition of this article is likely to have certain repercussions. Watch this space.

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1- "The Community legal order". In: K-D Borchardt "The ABC of Community law". Website <http://europa.eu.int/eur-lex/en/about/abc/index.html>



the national pharmacovigilance committee, yet none of these documents has yet been made public.

Thus, in 2005 the French Agency remained almost as secretive as it has always been. And by failing to transpose Directive 2004/27/EC in time and in full, the French health authorities are making it clear that the credibility of their regulatory agency is not a top priority.

The European Medicines Agency (EMA) is also highly inefficient. Regulation (EC) 726/2004 on the functioning of the European agency has come into force. By 20 November 2004, the Agency's management board was supposed to have defined how this Regulation concerning the Agency's functioning was to be applied.

The regulation concerning transparency should have been applied a year and a half ago, including article 73, which states that: "The Agency shall set up a register (...) to make available all documents that are publicly accessible pursuant to this Regulation". The EMA documents which, according to the Regulation, must be made public include: assessment reports on drugs approved by EMA; information on company withdrawals of marketing applications, along with the reasons for these withdrawals and the reasons for refusing marketing authorisation; a list of the conditions that companies must fulfill when conditional marketing approval is granted; information on serious adverse effects and other pharmacovigilance data; and statements of potential conflicts of interest by rapporteurs and experts of all committees; etc.

As of 6 December 2005, on the summary table on the Agency's website (<http://www.emea.eu.int>) entitled "EMA implementation of new EU pharmaceutical legislation", points concerning transparency, publication of information on withdrawals and denials of marketing authorisation, and pharmacovigilance communications, could be found at the end of the list. No application measures are announced.

Some small improvements have been made to certain documents that were generally available on the EMA website, but there is still no clear desire to make the Agency truly transparent.

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► 11.42 euros a day, compared to about 7.35 euros for an older low-molecular-weight heparin, despite no difference in efficacy or adverse effects (*La revue Prescrire* 257); fondaparinux was withdrawn from the market in February 2006; – the price granted to AstraZeneca for their product ximelagatran brings the daily anticoagulant treatment cost to about 5.70 euros, compared to about 0.23 euros for warfarin, a product with a far better risk-benefit ratio (*Prescrire Int* 78); – the price granted to Janssen-Cilag for injectable risperidone, brings the monthly treatment cost to 243.42 euros, compared to 8.74 euros for injectable haloperidol, which remains the standard neuroleptic (*Prescrire Int* 77); – treatment with aripiprazole (Bristol-Myers Squibb), costs nearly 20 times more than oral haloperidol, which remains the standard treatment (*Prescrire Int* 79).

No major price reduction when the target population expands. Not only are the prices of new products artificially high, but they almost never reduced when new indications are granted.

This was the case for the immunosuppressants etanercept, infliximab, leflunomide and adalimumab, when their approved uses in rheumatology were extended. The price granted to Serono for the latest immunosuppressant to be introduced, efalizumab, leads to a cost of 1087.00 euros for a 4-week treatment course for psoriasis, despite serious adverse effects and the lack of relevant comparative trials (*Prescrire Int* 81).

There are also several examples from the field of oncology, where indications can be upgraded from third-line to second-line to first-line treatment, and then to adjuvant therapy. For instance, in 2005, trastuzumab (Roche), cost about 2600 euros per month, even in adjuvant treatment of breast cancer (an off-licence indication in France but one that is widely promoted and practised despite ongoing unanswered questions; *Prescrire Int* 81).

In summary

The Health authorities seem to be more concerned with the economic health of the pharmaceutical industry than with public health. Patients and caregivers are counting on the authorities to return to their original mission: to protect public interests.

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