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**EDITORIAL**

# European and French pharmaceutical market assessed by Prescrire in 2005: mainly bogus innovation

At the beginning of every year, *Prescrire* (totally funded by subscribers, no advertising) takes a look back at trends in the French pharmaceuticals market, based on the results of our evaluations during the past year[1].

*Prescrire's* global assessment of new drugs and indications 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 balance, but also its advantages and disadvantages as compared to existing treatments available in France. Therefore, the relative value of new product can vary from one country to another. *Prescrire's* rating system is represented by the *Prescrire* gnome named "Gaspard Bonhomme", with following comments[2]:

—*Bravo*: the product is a major therapeutic advance in an area where previously no treatment was available.

—*A real advance:* the product is an important therapeutic innovation but has certain limitations.

—*Offers an advantage:* the product has some value but does not fundamentally change the present therapeutic practice.

—*Possibly helpful:* the product has minimal additional value, and should not change prescribing habits except in rare circunstances.

—*Nothing new:* the product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available (in most cases, it concerns a mee-too product).

—*Judgement reserved:* the editors postpone their rating until better data and a more thorough evaluation of the drug are available.

—*Not acceptable:* product whithout benefice but with potential or real disadvantages.

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* Awards list[3]:

—Chickenpox vaccine Varivax® is a real advance if restricted to specific groups of non immune immunocompetent adults who are in a position to transmit chickenpox to immunodeficient contacts (e.g. health care personnel and kindergarten staff); adults who have been in contact with a case of chickenpox within the past three days; and children in awaiting transplantation. Mass vaccination is not justifed, however, and far more data are needed on the balance of benefits *versus* harm in immunocompromised patients. The vaccine's adverse effects are acceptable.

—Pemetrexed offers an advantage in patients receiving first line chemotherapy for inoperable pleural mesothelioma: one trial suggest that the permetrexed + cisplatin combination prolongs survival about 3 month as compared with cisplatin alone (12 *versus* 9 months), but at a cost of frequent and severe additional adverse effects such as fatigue, leukopenia and neutropenia.

—Trastuzumab offers an advantage for women with metastatic breast cancer overexpressing HER-2 protein. A combination of docetaxel + trastuzumab prolongs survival by a few months compared with docetaxel monotherapy. Adverse effects, especially cardiac toxicity, have not been adequately documented. It is unclear whether docetaxel is the best cytotoxic agent for use in combination with trastuzumab.

—Zinc acetate offers an advantage in Wilson disease, in case of failure of – or intolerance to – penicillamine, or as first line treatment for asymptomatic patients.

Twenty new drugs or indications approved in 2005 offered limited advantages 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.

2005 also saw an increase in the number of new products that we found to be "not 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. These poorly assessed "innovations" have no proven therapeutic advantage over existing products but

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

| *Rating* | *Number* | *International non proprietary names (INN) and trade names* |
|---|---|---|
| Bravo | 0 | – |
| A real advance | 0 | – |
| Offers an advantage | 2 | Pemetrexed (Alimta®)[a], zinc (Wilzin®) |
| Possibly helpful | 5 | Bortezomib (Velcade®), fulvestrant (Faslodex®), insulin glargine (Lantus®), miglustat (Zavesca®), pregabalin (Lyrica®)[b] |
| Nothing new | 10 | Abacavir + lamivudine (Kivexa®), aripiprazole (Abilify®), bivalirudine (Angiox®), liposomal cytarabine (Depocyte®), fosamprenavir (Telzir®), pemetrexed (Alimta®)[c], pramipexole (Sifrol®), pregabalin (Lyrica®)[d], ranelate strontium (Protelos®), vaccine against cholera (Dukoral®) |
| Not acceptable | 8 | Celecoxib (Onsenal®)[e], cetuximab (Erbitux®), duloxetine (Yentreve®)[e], efalizumab (Raptiva®), ibritumomab (Zevalin®), rosiglitazone + metformin (Avandamet®), tasonermin (Beromun®), tolcapone (Tasmar®) |
| Judgement reserved | 1 | Porfimer (PhotoBarr®) |
| *Total* | *26* | |

a: Non resectable pleural mesothelioma; b: Neuropathic pain; c: Non small-cell lung cancer;
d: Combination therapy, epilepsy; e: Not marketed as of December 2005.

carry unjustified risks of serious adverse effects. Some examples include:

—Efalizumab, in plaque psoriasis: risk of skin cancer and potentially severe infections.

—Cetuximab, in colorectal cancer: risk of acne and hypersensitivity reactions.

—Radiolabeled ibritumomab, in some forms of non Hodgkin's lymphoma: complicates treatment and has disappointing efficacy and tolerability.

—Celecoxib was assessed for only 6 months, at a dose of 800 mg/day, in colorectal cancer prevention in patients with familial adenomatous polyposis.

—Duloxetine, in stress urinary incontinence: adverse effects include dizziness, nausea, hepatic disorders, suicide attempts, etc.

—Tasonermin, only fragmentary evidence of efficacy in soft-tissue sarcomas, but potentially serious and poorly documented adverse effects.

—Dactinomycin: this antibiotic, long used as a cytotoxic agent, is associated with haematological, gastrointestinal and hepatic adverse effects in most patients;

—Tolcapone 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.

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. The comparison of our conclusions with the French Transparency Committee's rating in 2004 showed that this Pharmacoeconomic Committee was less demanding than *Prescrire* and is less concerned with convenience of use[4]. 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[5].

Compared to 2004, more new drugs, new fixed-dose combinations and new indications were approved through the European centralised procedure in 2005: Thirty-nine centralised European marketing authorisations were granted by the European Commission, following the recommendations of the European Medicines Agency (EMEA) (see table I). 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[1].

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. The Cox-2 inhibitor saga continued in 2005. 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[6]. 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. Allergic reactions, thrombocytopenia, leukopenia and infections occurred with adalimumab. 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. New data on the cardiotoxicity of trastuzumab support those obtained in initial clinical trials, yet the French Agency has released little information (to healthcare professionals or patients), while at the same time extending the approved uses of these drugs.

In 2004 we wrote that drug prices have nothing to do with R&D costs and medical benefits[7]. Nothing much changed in 2005. 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 (which is often very lenient). 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. 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.

In summary, the French government seems 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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