Translated from *Rev Prescrire* **November 2005; 25 (266): 793-796**

# What matters most to the French regulatory agency: public health, or the health of drug companies?

*The September issue of your publication, particularly the editorial entitled "The French regulatory agency: where do its true priorities lie?" [see page 33], included a number of statements and insinuations that basically amounted to a form of character assassination, and seriously called into question the quality of the work accomplished by Afssaps (the French regulatory agency) on behalf of public health, as well as the professional reputation and public service motivation of the staff and experts who participate in drug assessment and decision-making.*

*The seriousness of these accusations, based on arguments unworthy of a public health debate and ignoring the rules of scientific debate, has led me to exert my legal right to respond (…).*

*Your editorial mentions the case of four products or groups of products. In at least one of these, Di-Antalvic° (dextropropoxyphene-paracetamol), you have not presented any solid arguments refuting the Agency's statements in support of its recent position. This example appears to have been tacked on at the last moment by an editor seeking simply to reach "critical mass".*

***Amalgamation.*** *By a process of amalgamation, the editorial paints a picture of an Agency whose decisions are influenced, or at least inhibited, by a wish to protect drug company sales.*

*The editorial and the article to which it refers to are full of paradoxical claims, going so far as to suggest that the Agency's decision to withdraw marketing authorisation for local oral antibiotics illustrates its presumed spinelessness and its deference to the companies concerned! As the decision itself can hardly be construed as being favourable to the manufacturers, the editor sees signs of the Agency's "weakness" in the separation of the two groups of withdrawals (in 2003 and 2005) and in the time taken to implement each group of withdrawals. At the time of the first withdrawals the Agency explicitly spelled out the public health concerns that led it to prioritise products associated with the greatest risks for patients because they contained antibiotics that were also administered systemically (not the case for Locabiotal°, for instance, one of the examples cited in your article). With respect to the chronology, drug companies in France, as in any other country respecting the rule of law, can defend their position by raising new arguments and by producing study data. As there was no immediate health risk for patients, the relevant task force and the marketing authority duly examined the manufacturers' successive arguments, as required within the rules of proper scientific debate. This did not influence the Agency's opinion nor undermine its determination to stop the use of these antibiotics. The public health rationale for these decisions has been praised by many consumers who are both impartial and unlikely to be suspected of deference to the health authorities.*

***Di-Antalvic°.*** *In the case of Di-Antalvic°, the Agency denies that the opinion of another national regulatory agency should automatically be accepted by the French Agency without first assessing its relevance to health care in France. The Agency clearly explained the rationale for its conclusions based on drug utilisation data in France (cf. press release dated 28 July 2005, available on the Agency's website).*

***Agréal° (veralipride).*** *As for the two products withdrawn by the Spanish agency in 2003, I would first like to point out that, in the case of Agreal°, Afssaps launched a pharmacovigilance survey in February 2005 and that, on 21 July 2005, recommended that the drug be kept on the market, on condition that a series of changes be made to the SPC (treatment limited to 3 months, contraindication of concomitant use with neuroleptics, antipsychotics and anti-emetics, reinforced warnings on the risk of dyskinesias and parkinsonian syndromes requiring treatment cessation, and the possible occurrence of mood disorders and anxiety, particularly between two courses of treatment or following discontinuation).*

***Mediator° (benfluorex).*** *In the case of Mediator°, several cases of amphetamine-like adverse effects reported in December 2004 led the Agency to update its data on neuropsychiatric disorders observed with this product. Last June, the technical pharmacovigilance committee examined the results of a study of the risks of pulmonary hypertension. They found a very low rate of reported events, around 1 case of pulmonary artery hypertension per 55 million boxes sold. These results will be submitted to the national pharmacovigilance committee next November.*

***Cox-2 inhibitors.*** *Finally, it is impossible not to react to the harsh claim that the Agency had decided to release as little information as possible on the risks associated with the cox-2 inhibitors. The editor seems to be unaware that it is Afssaps which requested a European-level re-assessment in mid-2002. The editor also forgot to mention the information and warnings published by the Agency since July 2002: no fewer than about ten press releases, five 'dear doctor' letters, and three updates or papers with a question-and-answer format.*

***Secrecy.*** *Finally, while it is true that the pharmaceutical tradition is strongly steeped in secrecy and confidentiality, and that this has had repercussions on the functioning of drug regulatory agencies worldwide, Afssaps is actively preparing to implement the new requirements for greater transparency included in the 2004 European Directive. Afssaps partly anticipated these new transparency requirements by starting to publish public assessment reports. These are intentionally written to be understandable to an informed but not necessarily specialised readership.*

*These transparency requirements are a step forward for Europe. They will in no way affect the French Agency's priorities, as stated in its mission statement. This was published in spring 2004. The aim is to ensure that patients' therapeutic needs are met under optimal safety conditions. One major Afssaps project that is already well underway is to provide continuous information on health products, their effects, and their proper use.*

*Thus, the Agency is working "in the open", in the best interests of public health and patients. It does not consider itself to be the sole holder and purveyor of pertinent information on medicines, whose evaluation is by nature an ongoing process requiring multidisciplinary expertise and open debate. It is in this spirit that many of Afssap's staff and managers pay attention to analyses made by journals like Prescrire. And they will be able to continue to do so as long as they find that decisions based on high-quality scientific work are cited, or at least as long as their desire to serve patients' interests and public health is not systematically called into question.*

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"*The work accomplished by Afssaps on behalf of public health*" and "*the professional reputation and public service motivation of the staff and experts who participate in drug assessment and decision-making*": it is precisely here that citizens, patients and healthcare professionals expect to see the results of the Agency's actions.

**Dextropropoxyphene + paracetamol.** Assessment data were reviewed by *Prescrire*: the dextropropoxyphene + paracetamol combination is illogical from a pharmacological standpoint (due to the large difference in the plasma elimination half-lives of the two compounds); comparative clinical evaluation showed no superiority of the combination over paracetamol alone; in the United Kingdom, hundreds of deaths due to overdose are recorded each year (combining paracetamol with dextropropoxyphene adds to its toxicity), and about 20% of these deaths are not due to deliberate overdose (even though packages are limited to no more than 20 dose units in the UK, as in France). There are similar reports in Sweden, where prescribing restrictions have not solved the problem, and market withdrawal is also planned. The Swiss regulatory agency discreetly withdrew this combination in 2003 (1-4). [See also page 20]

In summary, this product has a clearly negative risk-benefit balance: it is more dangerous than paracetamol alone but no more effective.

In these circumstances, how can clinical data in France possibly tip the scales in favour of this combination? At the time of writing (30 September 2005), the study based on data from French Poison Information Centres (mentioned by the Afssaps director general) has still not been published in full. We do not know how many deaths have been studied that are not due to intentional overdose, such as deaths among elderly people, many of whom use this seemingly harmless analgesic and are among those at greatest risk of accidental overdose (due to slow drug elimination). How many deaths among elderly patients treated with dextropropoxyphene appear to be due to natural causes or are attributed to heart disease, without a blood assay for dextropropoxyphene?

Moreover, even if this French study does not underestimate the number of deaths, how can anyone justify even 7 deaths a year due to a product that has no demonstrated advantage over the first-choice analgesic, paracetamol?

How can the authorities claim to be acting in the public interest when they allow people to be exposed to a dangerous drug without therapeutic advantages?

**Veralipride.** As to the efficacy of this neuroleptic in treating hot flushes associated with menopause, the French summary of product characteristics (SPC) refers to *in vitro* effects without supporting clinical data (5). *Martindale* states that veralipride has been "*tried*", but does not mention any convincing evidence of effectiveness (6). In 1983 the French SPC already stated that the adverse effects of veralipride were "*those of a neuroleptic*" (7). An established risk exists of adverse effects that are sufficiently severe to require long-term levodopa therapy (8). Spanish data and the decision taken by the Spanish authorities confirm that the risk-benefit balance of veralipride for treatment of menopausal hot flushes is sufficiently negative to warrant market withdrawal (9).

In these circumstances, how could the results of a pharmacovigilance study possibly be expected to tip the scales in favour of this drug? And what changes to the labelling would be sufficient to avoid the risks of extrapyramidal syndromes, which have been clearly mentioned in the SPC for more than 20 years?

How can the authorities claim to be acting in the public interest when they allow people to be exposed to a dangerous drug without therapeutic advantages?

**Benfluorex.** Benfluorex is an amphetamine appetite suppressant (10). When it was first marketed in France in 1976, it was "*proposed for*" hypercholesterolemia, hypertriglyceridemia and asymptomatic diabetes, the words "*proposed for*" meaning that these indications were not supported by evidence from clinical trials (11). Nearly 30 years later, the SPC still states that efficacy in primary and secondary prevention of complications of atherosclerosis has not been proven (12). Amphetamine appetite suppressants have been implicated in severe pulmonary arterial hypertension since the late 1960s (13), and the accompanying risk of cardiac valve disease was established in the late 1990s (13). Benfluorex was also implicated in cases of valvular disease necessitating heart surgery (10,13). Decisions taken in Spain in 2003 and 2005 confirm that the risk-benefit balance of benfluorex is sufficiently negative to justify market withdrawal of the product and prohibition of preparation of pharmacy compounds (14).

In these circumstances, how could a single pharmacovigilance survey, even if it included valvular disease (not mentioned by the Afssaps director general), tip the balance in favour of this drug?

How can the authorities claim to be acting in the public interest when they allow people to be exposed to a dangerous drug without therapeutic advantages?

**Cox-2 inhibitors.** The first worrisome evidence of cardiovascular risks associated with rofecoxib use were published in the VIGOR trial in spring 2000, as we reported in July 2000 (15). Detailed findings were released by the Food and Drug Administration in February 2001, along with data revealing how the results of the CLASS trial of celecoxib had been "massaged" (16). The first Afssaps press release concerning these two Cox-2 inhibitors was dated August 2001 (17). Afssaps requested a European-level reassessment in June 2002, fully 2 years after the first warnings were published, and *Prescrire* reported on this request in its September 2002 issue (18). Afssaps did not publish an assessment of this drug when it approved it for marketing in France. At the time of writing (30 September 2005), Afssaps has still not published detailed French pharmacovigilance data for these Cox-2 inhibitors, and has provided no estimate of the incidence of cardiovascular events due to rofecoxib use in France. Although the APPROVe trial (mentioned by Merck Sharp and Dohme-Chibret in support of worldwide market withdrawal in 2004) was partly carried out in France, Afssaps released even fewer relevant data than its British counterpart (19-21).

**Secrecy.** Dextropropoxyphene, veralipride and benfluorex: as expected, Afssaps has published no reports of the studies mentioned by its director general. The Afssaps 2004 annual report mentions 2940 periodic safety update reports (PSURs) sent to the French Agency, 43 files presented to the technical pharmacovigilance committee, and 18 files presented to the national pharmacovigilance committee; none of these documents has been made public (22).

While statements of conflicts of interest by Afssaps experts take up dozens and dozens of pages in an annex to the 2004 activity report, Afssaps has still published no reports of marketing authorisation committee or pharmacovigilance committee meetings, nor even a simple list of participants or agendas that would enable members of the public to verify that experts with conflicts of interest are actually excluded from meetings (23).

Is this what the Afssaps director general means by "working in the open"?

**Slowness.** When the regulatory agency takes decisions and carries out work ►►



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► that serves the public good, we report and praise these activities. Examples in 2005 include surveillance of devices, cosmetics, and products not requiring marketing authorisation, modifications in the SPC due to the results of pharmacovigilance, and drug packaging (24-30). But what is most striking about most of these decisions is the painfully slow speed at which they are taken.

Thus, in September 2005, the director general announced the market withdrawal of several ''immunostimulants", effective as of late October 2005. This is a very welcome measure. In November 2001 we reported on the Saint-Étienne regional pharmacovigilance centre's survey of French reports up to 1998, showing a risk of rare but serious adverse effects of these drugs (31).

Although these drugs were no more effective than placebo, why was their withdrawal announced 7 years after the last reports mentioned in the survey, and 4 years after results of the survey became available?

In the case of oral local antibiotics, why did the authorities exempt some non systemic antibiotics (only 12 products), if not to cushion the manufacturers? Yet how much more time did they really need, when for example Locabiotal° (a local oral spray) was already on the list of drugs providing "insufficient medical benefit" published in June 2001 by the French Transparency committee (32)?

**On whose behalf?** In each of these recent examples, the main beneficiary of Afssaps' excessive slowness, spinelessness and secrecy was the pharmaceutical company that marketed the product in question and whose sales continued unabated. The main victims were the patients who remained exposed to drugs with documented adverse effects and no therapeutic advantages. Indirect victims are uninformed caregivers, as well as Afssaps staff who are truly motivated by their public service mission but see their best efforts simply serving the special interests of pharmaceutical companies, who manage to postpone unfavourable decisions, even when there is a strong justification from a public health perspective.

Regulatory agencies must not be allowed to bend to pressure from manufacturers' lobbies nor from expert committees that are often timid and at times unduly influenced by manufacturers. The best decision, made in the public interest, may not be the one recommended by an unwise committee. Thus, in the spring of 2005, an expert committee convened by the FDA recommended that valdecoxib be kept on the market. Many of the experts had financial links to companies that held marketing authorisations for Cox-2 inhibitors. The FDA nonetheless decided that valdecoxib should be withdrawn (33).

**Decisive change.** Regulatory agencies throughout the European Union, especially those that seek to serve the public interest and uphold the law, have been required to apply Directive 2004/27/EC since 30 October 2005, whether or not it is transposed into national law. This Directive includes the following requirement (article 126b): "*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*". This is an excellent opportunity for the French Agency to show unambiguously that it is clearly patient-oriented, that it openly defends public health, and that it has corrected the flaws (delays, secrecy, etc.) that benefit the most influential drug companies. In the long term, a level playing field and clearly established rules are in the best interests of both patients and the pharmaceutical industry.

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