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Translated from ***Rev Prescrire*** **March 2005; 25 (259): 222-225**

How to avoid future Vioxx°-type scandals

The market withdrawal of rofecoxib (Vioxx°) in September 2004 was the logical, if long-overdue, result of what has become a major scandal. How can similar situations be avoided in the future? The authorities must of course come to grips with their responsibilities, but caregivers, patients and journalists also have a role to play. This was the theme of the press conference held at Prescrire headquarters after the annual awards ceremony on 20 January 2005.

The withdrawal of rofecoxib (Vioxx°) in September 2004 was the predictable result of major flaws in current regulations governing drug evaluation, market control, and medical information.

What exactly happened?

Rofecoxib was first approved in the United States, in May 1999 (1), and then in France in November 1999 (2), mainly for symptomatic relief of osteoarthritis. The company was targeting a vast market with this drug, as a large proportion of the population in rich countries suffers from osteoarthritis. Rofecoxib was not a cure, but rather provided temporary relief.

The company's massive advertising campaign touted rofecoxib as "revolutionary", based on its claimed gastrointestinal safety (3). In France, treatment was about five times more expensive than with ibuprofen 1200 mg/day when obtained from retail pharmacies, but cost only a fraction of a euro cent per day when obtained from a hospital pharmacy; the company sold the drug to hospitals at a low price in order to benefit from the prestige associated with hospital prescription (4).

No proof of a therapeutic advantage. Clinical trial data focused on a claimed advantage in terms of gastrointestinal adverse effects (2). However, the evidence was unreliable, as it was based on flawed comparisons. The manufacturer failed to compare rofecoxib with paracetamol (the first-line analgesic for osteoarthritis); or with ibuprofen 1200-1600 mg/day; or with NSAID + protection against gastric ulcers (2,5).

Non-gastrointestinal adverse effects were poorly reported, but the first US summary of product characteristics (SPC) already mentioned a higher incidence of hypertension with rofecoxib than with the classical NSAIDs with which rofecoxib had been compared (6).

The Vigor trial: an increase in myocardial infarction. The first results of the Vigor trial, involving patients with rheumatoid arthritis, were reported at a British conference in May 2000 (5), and showed an increase in cardiovascular events in patients taking rofecoxib.

In February 2001 the FDA conducted a detailed analysis of Vigor trial results and cardiovascular data provided by the company (7). Globally, the results of the Vigor trial were unfavourable for rofecoxib (see table below). The lower frequency of serious gastrointestinal adverse effects on rofecoxib was cancelled out by an increase in serious cardiovascular events.

Controversy and time-wasting. The company then suggested that naproxen, the drug with which rofecoxib was compared in the Vigor trial, protected patients against cardiovascular disease, although none of the data held by the FDA supported this claim (7). Rofecoxib was nonetheless approved for patients with rheumatoid arthritis in the United States (1) and then in France (8). At that time the French pharmacoeconomic Committee [that assesses medical benefits of new drugs with a view to reimbursement] stated that the excess risk of cardiovascular events had not been convincingly established, mainly because these adverse effects were not a primary outcome of the Vigor trial (9). The global results, especially the mortality rate, were simply overlooked.

Meanwhile, sales continued unabated. In France, health insurance reimbursements for rofecoxib reached approximately 116 million euros in 2002 and 125 million euros in 2003 (10,11).

In France, a postmarketing study called Cadeus, designed to evaluate the characteristics of users of NSAIDs, especially Cox-2 inhibitors, was launched in September 2003, with results expected in March 2005 (**a**)(12).

Abundant evidence, feeble decisions. In April 2004 the European Medicines Evaluation Agency (EMEA) announced that it had reviewed all available data on the Cox-2 inhibitors, and that "*available data indicated that significant and consistent gastrointestinal benefit of Cox-2 inhibitors compared with conventional NSAIDs has not been demonstrated*". As to cardiovascular effects, the Agency stated: "*Cox-2 inhibitors had no antiplatelet effect in therapeutic doses. With respect to cardiovascular risk, it can be considered that there may be a small safety disadvantage of Cox-2 inhibitors compared to conventional NSAIDs*" (13,14). However, the EMEA failed to suspend marketing authorisation for these drugs. The only measure taken was to reinforce the relevant warnings on the SPC.

The French regulatory agency simply followed the European agency's ineffectual lead. The French pharmacoeconomic Committee stated that rofecoxib had only a "minimal" advantage in terms of gastrointestinal adverse effects, and repeated that evidence for an excess of cardiovascular events in the Vigor trial was weak (15).

The French government did not even lower the price of rofecoxib (16).

A trial with overwhelming evidence. In September 2004 the manufacturer announced the premature termination of a clinical trial testing rofecoxib for the prevention of complications associated with colonic polyps, on the basis of appalling preliminary results: there were an extra 7.5 serious cardiovascular events per 1000 patient-years in the rofecoxib group compared to the placebo group, which is about the same percentage of cardiovascular events prevented by drug therapy for hypertension (17,18).

An American team recently estimated that about 30 000 cases of myocardial infarction and sudden death are attributable to rofecoxib in the United States alone, excluding strokes (18). The French agency has published no estimate of the number of cardiovascular events due to rofecoxib use in France. ►►

a- As of early 2005 the website of the Cadeus study sponsor did not provide the study protocol or the funding sources. The list of partners omitted MSD and Pfizer, both of which are mentioned in the ethical opinion given by the Conseil national de l'Ordre des médecins (available on the sponsor's website).

PATIENT SAFETY

Public health oriented authorities are needed

Health authorities, caregivers, patients and journalists alike can all help to prevent new scandals of this type.

Public health and patient interest are not companies' chief concern. The teams who publish *Prescrire* and many other independent drug bulletins worldwide examined the initial evidence on rofecoxib from the patient's point of view and found the issue perfectly clear as early as 2000: in the case of a non life-threatening condition for which several treatments are already available, there is no reason whatsoever to run a risk of serious cardiovascular events with a new drug that has no proven advantages.

If the authorities had applied this basic principle, tens of thousands of deaths and heart attacks due to rofecoxib might have been avoided.

Demand proof of therapeutic advantages. Wealthy countries (United States, Japan, EU member states, etc.) have never demanded proof of therapeutic advantage before approving a new drug.

Pharmaceutical companies need only prove their product has an acceptable risk-benefit balance. The International Conference on Harmonization (ICH) acts as a forum issuing guidelines for representatives of drug regulatory agencies and drug companies. The stated aim is to simplify, standardise and, especially, accelerate the processing of marketing applications; this of course implies that the quality of the assessment is a secondary issue. In fact, the main beneficiaries of the ICH setup are not the health authorities, or the public, but drug companies themselves. It is therefore not surprising that the ICH is run by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (19,20).

Drug regulatory agencies in bed with drug companies. Regulatory agencies' main "clients" are drug companies seeking marketing approval and changes to licensing. Drug companies are also regulatory agencies' main funding source (more than 50% of total revenue), principally in the form of application fees (21). In addition, many outside experts work for both regulatory agencies and drug companies (22,23). Given this situation it is hardly surprising that the EMEA is governed by the EU Commission's Enterprise Directorate-General rather than the Health and Consumer Protection Directorate-General.

Free access to clinical data. There is nothing in the current regulations to prevent regulatory agencies from opting for transparency if they are really concerned about public health.

There is no legal reason why they should not publish all the clinical data they currently hold. Although clinical research is funded mainly by pharmaceutical firms, the results of such studies belong as much to the patients who agree to participate as to the sponsor. And let's not forget that it is society as a whole that pays for health services and thereby enables drug companies to obtain a return on their investment. There is no legal or ethical reason why all the information that applicants provide to regulatory agencies, including postmarketing drug safety data, should not be made public. The FDA already partially publishes postmarketing data on a large number of drugs, and other agencies could follow this lead if they so desired. What is more, the new European regulation actually encourages them to do so.

Applying the new European regulation. The French agency must apply Directive 2004/27/EC by October 2005 at the latest, including article 126b, which stipulates that: "*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*" (24).

Since 20 November 2004 the EMEA has had to comply with Regulation (EC) 726/2004, especially article 73 relating to the European Regulation on public access to documents, stating that: "*The Agency shall set up a register (...) 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*" (24).

If regulatory agencies themselves are unwilling to stand up to drug companies, or to issue critical appraisals of data, then they should at least let independent organisations evaluate these data.

Active, transparent and publicised postmarketing pharmacovigilance. It would be a simple matter for health authorities to set up an efficient system for monitoring adverse effects in order to determine the precise risk-benefit balances of the drugs they license.

In France, if the authorities are really concerned with preserving and improving public health, they should provide regional pharmacovigilance centres with adequate funding so that they can properly analyse and publish their results; encourage reporting by health care professionals (beyond simple legal obligations); organise the collection and analysis of direct reports by patients; analyse and publish regional data collected by health insurers; and fund more epidemiological studies.

The French agency's annual report for 2003 mentioned grants of only 3.5 million euros for these centres (22), which is a tiny fraction of the 125 million euros reimbursed to rofecoxib users (11).

The 2003 report also lists 322 Periodic Safety Update Reports (PSURs) sent to the French agency, none of which have been made public; 45 market applications examined by technical committees, none of which have been made public; and 19 files examined by the national agency, only scraps of which (concerning the hepatitis B vaccine) are publicly available (22,25).

Health care professionals must work in total independence

Pharmaceutical firms are hardly in a position to provide objective information on the drugs they manufacture and sell.

The Vioxx° scandal once again demonstrates that regulatory agencies are mostly preoccupied with the problems of drug companies (with whom they are in constant contact) and are relatively insensitive to the concerns of patients and public health. The author-

ities react far too slowly to significant pharmacovigilance alerts, and then only with feeble half-measures, leaving prescribers at risk of choosing treatments with negative risk-benefit balances and patients at a risk of unnecessary adverse effects or even death (26). Other drugs associated with serious adverse events before they were belatedly withdrawn from the French market over the last decade include Atrium° (febarbamate + difebarbamate + phenobarbital), Prepulsid° (cisapride), and Teldane° (terfenadine).

Marketing approval protects drug companies and regulatory agencies, but not prescribers. If prescribers base their treatment decisions solely on drug companies' inflated claims and on questionable approval decisions, while at the same time trusting regulatory agencies to react in a timely manner to drug safety alerts, they run a risk of legitimate legal actions, which they will have to face alone.

All health care professionals must place their patients' interests uppermost, demand firm evidence of therapeutic advantage before prescribing new drugs, and base their decisions on independent information sources.

Health care professionals must learn to say "Thanks, but no thanks" to drug company sponsorship of academic and continuous professional training, and must refuse drug company access to their hospitals and practices. They should opt for independent training programmes as many of their colleagues have already done (27-30).

Patients must remain alert and begin to take collective action

Patients must realise that, as things stand now, most new drugs offer no therapeutic advantage whatsoever, and that some even represent a step backwards. They should also be aware that new drugs carry a danger of unidentified adverse effects, and that older, well-evaluated drugs remain the unchallenged standard of treatment for many conditions (31).

Patients should know that drugs are promoted using the same advertising methods as those used for consumer goods, including "opinion leaders" who are little more than drug industry puppets, and biased media reports (32-35).

They should also realise that regulatory agencies are slow to react to drug safety warnings, and may leave drugs with negative risk-benefit balances on the market for a number of years.

They should select health care professionals who opt for independent professional training programmes, and should act collectively to demand more transparency from regulatory agencies, funding of truly useful clinical research.

Journalists who are determined not to spread disinformation must examine drug companies' claims with a critical eye; assess new drugs in the light of existing knowledge; reveal all conflicts of interest; demand more information from regulatory agencies; and check their information with independent sources (34,36-38).

We all need to react

Both the cerivastatin affair and more recently, the Vioxx° scandal illustrate the inadequacy of current rules governing marketing approval: the majority of resources available for clinical research are devoted to topics that bear little relation to public health. This leaves patients exposed to a risk of adverse effects when they take drugs that have not been properly evaluated. This situation is especially unacceptable when valid alternative treatments exist.

The Vioxx° scandal once again places the spotlight on the inadequacies of health authorities, with drug regulatory agencies often taking years to react to signifciant pharmacovigilance alerts.

The Vioxx° scandal also illustrates the consequences that ensue when the authorities fail to take therapeutic advantages into account when setting drug prices.

This is why a major upheaval of the criteria required for marketing approval is likely to be a more important way to avoid future drug safety disasters like Vioxx° than an increased number of postmarketing studies.

Meanwhile, if they are truly concerned with public health, regulatory agencies should break out of drug companies' hold, shake off their addiction to secrecy, and opt for measures that promote transparency and patients' interests. Not only would they become more credible and trust-worthy; they would also begin to truly act in the public interest.

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