Failure in drug safety assessment: a worrying issue far beyond manufacturer's potential conflicts of interest

In mid-80, at a DIA meeting, I made a short communication to express my concern about the methodological orientations of drug monitoring [1]; at the end of the conference, I met a now former responsible of the FDA who told me gently: "I do hope that your message will be received". Twenty years later, whereas I still have not determined whether this comment was ironical or not, I am sure that the "message" was not received, as exemplified by the increasing rate of dramatic drug withdrawals at a maximum human and financial cost, for not to speak about manufacturers image.

In a convincing investigation, Psaty et al (JAMA, 1 Dec 2004, 2622-2631) demonstrated that clues of cerivastatin-related muscular toxicity were detectable long before world withdrawal. Actually, in my experience of consultant, I never saw a hazard requiring drug withdrawal which was not detectable (or, at least, likely to induce a strong degree of suspicion) during the phases of development. Nevertheless, an important point was overlooked by Psaty et al: as the scandal surrounding cerivastatin withdrawal was unusually high, regulatory authorities would certainly have pointed out to Bayer's responsibility if they had any pretext to do so. As this was not the case, the only credible conclusion is that in spite of its now documented poor performance, the manufacturer' job complied with current regulatory guidelines and everyday practices in the field of drug monitoring. This worrying record is only one amongst a lot of others: e.g. a similar study showing that rofecoxib should have been withdrawn earlier [2] or increasing evidence on the inappropriate behaviour of FDA officials when they are confronted to significant safety alerts (SCRIP Nov 24th 2004, 14-16). In Dec 2001, the French Agency released on its website a report showing that it took some two years to the European CPMP to finalise a quite elementary contra-indication about cerivastatin-gemfibrozil combination, *versus* 8 months only to register the 0.8 mg dose (in a time where it was possible for the least to suspect the risks related to high doses!) Then, we are led to the sad conclusion that regulatory bodies are currently unable to guarantee the protection of public health as far as a fair assessment of drugs benefit/risk ratios.

This is not a scoop: how to give drug regulators any credit for consistency when, in a France, 3 published cases of drug liver toxicity of problematic causality were sufficient to withdraw a drug such as Tasmar® used in severe indications bearing a very high degree of risk, whereas the French Agency – and other "experts" – may advocate universal hepatitis B immunisation in very low-endemic countries while confessing that this vaccine induced "the greatest series of reporting collected since the system of drug monitoring was created" (Dartigues et al's report, Feb 2002)? How to rely in any way to methods of drug monitoring which regularly now lead investigators to put the stress more on "rhinitis", "gastralgia", "libido problem" or "hip surgery" than on significant clinical or laboratory hazards, to focus overall safety evaluations on the "emergent events" reported with (or even: ascribed to!) placebo, and to conclude without laughing that, quite often, the incidence of adverse "events" was fairly less on the active drug than on placebo?

The abovementioned communication [1] asked whether post-marketing surveillance was "an art or a science": no doubt, twenty years later, that drug monitoring is just playacting, which may evolve in tragedies.

Competing interest : Dr Girard works as an independent consultant for pharmaceutical industry and as a medical expert witness.

[1] Girard M. Post-marketing surveillance: an art or a science? Drug Inf J 1986;20:347-349

[2] Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of vascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; 364: 2021-2029