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Post-market studies: broken promises

For the past several years in France and internationally, there has been increased attention to post-market studies and clinical trials. There are various reasons for this trend; for example, drug regulatory agencies may want pharmacovigilance data or additional information on the risk-benefit balance and cost-effectiveness of a drug under real conditions of use. The increased frequency of conditional and fast-track (or even premature) marketing approval, often accompanied by requirements for manufacturers to conduct additional post-market research, is another explanation.

United States: unmet commitments. The United States Food and Drug Administration (FDA) regularly publishes information on the post-market studies that drug companies have promised to conduct (a). On 30 September 2005, the FDA listed 1552 ongoing commitments. Among these 1552 studies, 915 (59%) had not started, 325 were ongoing (21%), 81 had been postponed (5%), and three had been abandoned; 228 reports (15%) had been submitted to the FDA (1).

Since 1992, 42 (46%) of the 91 trials that manufacturers had agreed to conduct after receiving fast-track approval had not yet been completed (2) and 21 had not even started, even though the drugs were already on the market (for nearly 7 years in one case) (2).

Manufacturers that agree to conduct post-market studies must also provide the FDA with yearly progress reports (3). However, 35% of the 336 reports of this type that were due in 2004 were not filed (3). And 30% of the 778 annual reports submitted since 2004 lacked required information (3).

The FDA considers that it does not have sufficient legal grounds to enforce these commitments (3).

No better in France. In France, in May 2006, a team reviewed 105 studies requested by the French drug pricing and reimbursement committees since 1997 (b) (4). Only 7% of these studies had been completed, 54% had not yet begun (no documents had been received in 30% of cases, and the protocol was being validated in 24% of cases), even though one-third of these requests dated back to before May 2005 (4). The French Senate committee that investigated the conditions under which drugs are approved considered these results "mediocre" (4).

Don't count on post-market evaluation. Indeed, post-market studies, including clinical trials, are important for refining the risk-benefit balance of drugs under real conditions of use, especially as many pre-market trials are conducted in hospitals or in highly selected populations. But drug companies' broken promises, in France as in the United States, show that even when there are legal obligations, post-market studies are no substitute for proper pre-market evaluation.

The right time for drug regulatory agencies to obtain information from manufacturers on the risk-benefit balance and cost-effectiveness of a product is when they are examining the marketing application. Once approval has been granted, the balance of power shifts, allowing manufacturers to escape commitments or delay them to the detriment of patients, while they continue to promote sales.

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a- Drug companies' "commitments" are obligatory when a drug is approved under the fast-track procedure; otherwise, they result from a voluntary agreement with the FDA (ref 3).

b- There are no reviews of commitments made at the time of marketing approval. Conditional authorisation is subject to post-market trials, and should become more common in the European Union since the Regulation on human medicines was adopted (ref 5).

Selected references from Prescrire's literature search

1- Department of Health and Human Services. FDA "Report on the performance of drug and biologics firms in conducting postmarketing commitment studies; availability" *Federal Register* 2006; **71** (42): 10978-10979.
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4- Hermange MT et Payet AM "Rapport d'information fait au nom de la commission des Affaires sociales sur les conditions de mise sur le marché et de suivi des médicaments" Sénat 2006: 105 pages.
5- Prescrire Editorial Staff "Conditional marketing authorisation in the EU: an improved regulation if properly applied" *Prescrire Int* 2006; **15** (85): 199.