Protective measures adopted by the French regulatory agency but undermined by the European Medicines Agency

European legislation provides for an arbitration procedure for drugs marketed in one or more member states, notably at the request of a national agency citing serious harms, or following withdrawal (or intended withdrawal) by a national agency based on the pharmacovigilance data.

Despite several such procedures initiated by the French Health Products Agency, EMA is still taking too few effective measures to protect patients. EMA recommendations are often limited to simple changes in the summary of product characteristics (SPC), such as restrictions on use, reinforced warnings, instead of marketing authorisation withdrawal, even for products with an unfavourable harm-benefit balance. The final decision lies with the European Commission, but it usually just rubber-stamps the EMA recommendation.

This was the case in 2013 for an *ethinyl oestradiol + cyproterone* combination (Diane 35°), which was taken off the French market because of a disproportionate risk of thromboembolism when used off-label as a contraceptive and only modest efficacy to treat acne; yet EMA concluded that it had a favourable harm-benefit balance in patients with acne (*Prescrire Int* n° 139). Similarly, the French marketing authorisation committee recommended that *trimetazidine* be taken off the market. However, after conducting a reassessment, EMA concluded that the harm-benefit balance of *trimetazidine* remained favourable in some types of angina pectoris and therefore did not recommend market withdrawal (*Rev Prescrire* n° 357).

Healthcare policy must be more patient-centred

For several years now, *Prescrire*'s annual reviews have highlighted the paucity of therapeutic progress and the inadequacy of patient safeguards, against a background of industry pressure to increase drug sales.

Some decisions taken by a number of health authorities in 2013 appeared to put patients' interests first, but they were few and far between.

Too many drugs are authorised despite inadequate and, in some cases, deliberately biased assessment. A new European regulation on clinical trials will soon be adopted, providing an opportunity to improve the transparency of company-sponsored clinical trials (see english.prescrire.org).

Real progress will only be possible if regulations refocus clinical research on patients' real needs, improve the evaluation of new drugs, and put an end to the profitability of drugs that provide no advantages over existing options.

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Clinical trial rigging: again!

In 2013, several publications of trials assessing *valsartan* were retracted by the journals concerned, because the clinical data had been falsified (**a**)(1,2).

Overly favourable results... The results of a randomised comparative trial published in 2009 appeared to show that *valsartan* was highly effective in preventing angina and stroke, while results from previous trials showed that it only had a small effect (3,4).

In early 2013, this article was retracted by the European Heart Journal (published by the *European Society of Cardiology*), on account of "*critical problems*", as were other articles by the same Japanese author (1).

...but they had been tampered with. Following an investigation, the Japanese university that employed the author, who subsequently resigned, revealed that the raw data had been falsified to exaggerate the drug's benefits in preventing angina and stroke (3). The investigation also revealed that one of the persons involved in the trial was working for Novartis, the company which markets *valsartan*, although this affiliation was not disclosed in the published article (3).

The investigating committee repeated the statistical analyses, excluding patient data identified as having been falsified: the amended results showed that *valsartan* did not prevent angina or stroke (3).

Systemic problem. Following this initial scandal, *The Lancet* retracted an article on another trial of *valsartan* conducted in Japan, which again had not disclosed the involvement of a Novartis employee (2).

These scandals highlight many flaws in the current clinical research system, such as major, but undisclosed, conflicts of interest; academic authors deprived of access to the raw data; insufficient verification of scientific publications; low-key and inexplicit retractions of articles; and long delays before fraud is discovered.

Clinical research is almost exclusively funded by the pharmaceutical industry and, given the interests at stake, there is a risk of serious distortion of the facts.

In practice. *Prescrire* assessed *valsartan* before these articles were published, and its conclusions remain valid. These scandals serve as a reminder that clinical trial results are not an inviolable truth. There is always a possibility that these results will be called into question.

a- *The retraction of these articles is recorded in bibliographic databases and on the websites of the journals involved.*

Selected references from Prescrire's literature search.

1- Barthélémy P "Scandale autour d'un médicament vedette contre l'hypertension" 21 July 2013. http://passeurdesciences.blog.lemonde.fr accessed 27 August 2013: 2 pages.
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3- Komiyama R et al. "University admits clinical study of hypertension drug rigged" 12 July 2013. http://ajw.asahi.com accessed 27 August 2013: 2 pages.
4- Sawada T et al. "Retracted: Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: Kyoto Heart Study" *European Heart Journal* 2009; **30**: 2461-2469.