To:
The European Ombudsman, The European Union

Appeal concerning denial of access to clinical study reports and corresponding trial protocols at the European Medicines Agency

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We have previously applied twice for access to the clinical study reports of the placebo-controlled clinical trials and corresponding trial protocols of the anti-obesity drugs, orlistat and rimonabant, submitted to the European Medicines Agency (EMEA) for marketing approval.

EMEA did not grant us access to these documents and EMEA has explained on both occasions that we were denied access because of the exceptions listed in article 3.2(a) of the Rules for the Implementation of Regulation (EC) No 1049/2001. However, contrary to our explicit request in our second letter to EMEA, EMEA did not give any reasons why EMEA felt that commercial interests should override concerns for the welfare of the patients, although we had explained in our letter why EMEA's attitude increases the risk that patients die because of the treatments their doctors prescribe to them out of ignorance about what the true ratio is between the benefits and harms.

We have carefully argued why concerns for the patients' welfare should be given priority over concerns for the drug industry's commercial interests. Doctors get information about drugs by reading reports and reviews of randomized clinical trials in medical journals, but it has been shown repeatedly that such articles tend to exaggerate the benefits and to downplay the harms of drugs, compared to the study reports and trial protocols that have been submitted to agencies such as EMEA when companies apply for marketing approval.

The systematic distortion of the evidence about drugs in the public domain can have serious consequences for the patients. The anti-arthritis drug Vioxx, which was withdrawn from the market in 2004 as it causes heart attacks, has likely caused about 100,000 unnecessary heart attacks in the USA alone (1) (which corresponds to about 10,000 unnecessary deaths). Merck, the maker of the drug, concealed this harm for several years. By comparing published trial reports with documents submitted to the Food and Drug Administration in the USA (FDA) on the same trials it has been shown that several cases of sudden cardiac deaths and of non-fatal myocardial infarction on Merck's drug were omitted from the published trial reports (2-6). An editorial in The Lancet concluded: "with Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest" (7).

There is an abundance of other research that substantiates these examples. On several occasions, the public only learned about the problems because scientists at the FDA, or independent researchers who had access to files with the FDA, pointed out that what was published was flawed. For example, a pivotal trial report on another anti-arthritis drug, celecoxib, reported misleading short-term data in violation with the trial protocol (8). This drug also causes

heart attacks, although, as in the Vioxx case, the company, Pfizer, denied this fact for a long time before it was revealed by independent researchers who had access to the files at the FDA (9).

In 2005, an FDA advisory committee recommended approval of an anti-diabetic drug, muraglitazar, but independent researchers who analyzed the clinical trial data that the company had submitted to the FDA, revealed that the company had produced seriously flawed analyses, and that the drug was harmful, as it increased the risk of the composite outcome death, myocardial infarction or stroke (10,11).

We have already described in our letters to EMEA that a statistician working at the Swedish Drug Agency has shown that published trial reports of antidepressant drugs are seriously flawed, compared to the study reports that had been submitted to the agency when the companies applied for marketing approval (12). FDA reviewers and independent researchers have shown that several companies have concealed cases of suicidal thoughts in people receiving an antidepressant drug by labelling such cases as "emotional instability" (13,14). Furthermore, some cases of suicide and suicide attempts in patients in the placebo arm of the trial should not have been included, as they did not occur while the patients were randomized to the placebo (15,16). A systematic review showed that when unpublished trials were included, the conclusion about the benefits for several of these drugs changed considerably, from having a favourable risk-benefit profile to having an unfavourable one (17).

In another case, where a trial had shown that a long-acting drug against asthma, salmeterol, increased the number of deaths related to asthma, the company had manipulated the data it submitted to the FDA and it was concluded that "In the absence of the transparency associated with the Advisory Committee meetings, these deceptions would never have come to public attention" (18).

In the second letter from EMEA we were informed that EMEA publishes on its website the outcome of scientific discussions on the various drugs. We were aware of this, but these short summaries are not sufficient for an independent evaluation of the trials that have been submitted to EMEA. Quite obviously, full access to the clinical study reports and corresponding trial protocols are needed for such an evaluation. The protocols and the clinical study reports contain information about study design, including criteria for selection of patients, outcomes to be measured and methods for statistical analysis. This information is crucial for the interpretation of the results. Furthermore, many trial reports, in particular those with less impressive results, never get published.

The second letter from EMEA also states that the efficacy and safety of all medicines is being monitored. Again, and as our examples above demonstrate so clearly, this is not sufficient for doctors who wish to select the best possible treatments for their patients. For example, monitoring reported adverse effects reported by doctors to drug regulatory agencies would not have revealed that Vioxx causes heart attacks. Less than 10% of such events are ever reported, and heart attacks are common in people who use anti-arthritis drugs. It is therefore not possible by monitoring the use of drugs to detect if treatment with a certain drug leads to more heart attacks than one would expect. This can only be detected reliably in randomized clinical trials where the control group does not receive the drug in question.

We find the letters from EMEA wholly unconvincing, and we therefore appeal to the European Ombudsman that it should not be accepted that EMEA prioritises to protect the commercial interests of the drug companies, rather than protecting the lives and welfare of the patients. In particular as there appears to be nothing of commercial interest in the study reports and protocols. We have previously reviewed a large number of trial protocols of industry-initiated trials, approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg in Denmark, and we found

that what the companies published was a seriously biased selection of all the data that had been gathered in these trials (19). We believe that none of the protocols disclosed anything that could undermine the protection of commercial interests of a natural or legal person, including intellectual property. Apparently, the Scientific-Ethical Committees came to the same conclusion, or they at least concluded that there was an overriding public interest in our research.

The secrecy in drug regulation that EMEA prefers clearly leads to harm, including unnecessary deaths among patients and a huge waste of limited resources on drugs that appear to be better than currently used drugs, but many of which are in reality not better when subjected to the type of scrutiny that is only possible if access to trial protocols and clinical study reports is provided. We believe this attitude is ethically indefensible, as the prime duty of drug agencies is to protect patients from unnecessary harm. Disclosing the type of data that we are applying for would, as a general principle, not be anti-competitive, as all companies will be affected equally by it. But it would lead to more transparency, more rational use of resources, and less harm. And, to quote a person that has been involved with drug regulation: "Since the markets for drugs in most countries depends largely on public resources, the public should have access to data of interest" (20). We wish to add that drug trials cannot be performed without the altruistic contribution of the patients enrolled in them, and the patients should therefore have access to data of interest for them.

We also ask the Ombudsman to consider particularly carefully that drug regulatory agencies have a conflict of interest when they deny others access to the data in their possession. As expressed by the drug regulator: "The only reasonable explanation for the reason for such confidentiality that I can work out, however, is that the industry wants to avoid any discussion of the data they provide to justify the marketing of drugs. There is also the complicity of the regulatory agencies, that have access to the data, but avoid making it public, possibly so as not to be questioned over their decisions"" (20).

We attach our two letters to EMEA and EMEA's replies for information.

Yours sincerely,

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