To:
P. Nikiforos Diamanduris
The European Ombudsman
The European Union

Reply to the opinion provided by the European Medicines Agency (EMEA) to the European Ombudsman, regarding our appeal concerning denial of access to clinical study reports and corresponding trial protocols of anti-obesity drugs orlistat and rimonabant

Complaint 2560/2007/BEH

From:
Peter C Gøtzsche, director, DrMedSci, MSc, pcg@cochrane.dk
Anders W Jørgensen, MD, PhD student, awj@cochrane.dk

The Nordic Cochrane Center, Rigshospitalet, Copenhagen Denmark
www.cochrane.dk

19 May 2009

We herewith send our observations on the two letters from EMEA to the Ombudsman dated 26 February 2009 (EMEA/110754/2009) and 7 April 2009 (EMEA/213195/2009).

In the letter from 26 February, EMEA comments on a) *Aspect of commercial confidentiality of the clinical study reports and corresponding protocols*. They claim that competitors can use the documents as a basis to start developing the same or a similar medicinal product for their own economical advantage and get valuable information about the company's long term clinical development strategy.

However, the documents represent the last phase of the development of a drug, the clinical trials in patients. These trials have been preceded by many years of preclinical development, including in vitro and animal studies, pharmacokinetic and pharmacodynamic studies in healthy volunteers, and uncontrolled phase II studies in patients. Therefore, we find it very hard to believe that the documents could have any use for other companies as regards starting to develop a similar drug. In fact we believe that, compared to the documents that we have requested, the published papers in scientific journals of in vitro, animal and early studies in humans would be more relevant for other companies to know about. Since drug companies have no problem with publishing such studies, in fact they see an advantage in doing it as it might attract investors, we believe EMEAs argument has no merit at all. Finally, as unpublished trial data are less positive than those that are published, competitors would be less likely to start developing similar drugs, if they had access also to the unpublished data.

We also believe EMEA is wrong, when they claim that the requested documents fall into one or more of the three categorises in their definition of commercially confidential information (Intellectual property, trade secrets and commercial confidences). Firstly, the

documents are based on general and well-known principles that can be applied to any drug trial, which therefore cannot be patented. Secondly, the clinical study reports are about the clinical effects of drugs and nothing in the guidelines for clinical study reports (available in EMEAs letter to the Ombudsmand 28 April 2008) indicates that any information included there could be considered a trade secret. Thirdly, protocols are always sent to all the collaborating clinical investigators, and if the companies feared that they contained anything that might be of commercial value (e.g. a description of how the drug is synthetised), it is highly unlikely that they would not remove these particular parts from the protocol. We have previously reviewed many industry-initiated trial protocols and we did not find anything that could be considered a trade secret.

EMEA also comments on b) *Evidence of an overriding public interest in disclosure.* They are of the opinion we have not proved that lives will be saved if we get access to the documents. Of course we cannot prove this in the concrete case because we are denied access to the evidence! However, in previous letters to EMEA we have documented that published reports of industry-conducted trials are biased, and they are therefore clearly insufficient for practicing clincians when they make decisions and for researchers when performing systematic reviews and meta-analyses of the clinical trial evidence. In other words, if doctors only rely on published information, patients will not be treated optimally and some will die unnecessarily, as recent cases have demonstrated. We mention here as an example the case of COX-2 inhibitors.

Merck concealed cases of myocardial infarction and deaths from rofecoxib, which were missing in reports of the pivotal trials (1-4). This misconduct led to the unnecessary deaths of thousands of patients (5)(6). New York Times reported that Pfizer denied that celecoxib causes heart attacks at a hearing with the FDA (7), and Pfizer also denied this in "Dear Doctor" letters (personal observation from Denmark; we have a copy of this letter), despite having unpublished evidence to the contrary (7). Pharmacia, which was later bought by Pfizer, published seriously misleading 6-month data in two pivotal trials of celecoxib, in violation with the trial protocol (8)(9). The published trials showed that celecoxib results in less gastrointestinal ulcers than its competitors, but it was later revealed that the trials ran for longer than 6 months, and that analyses done according to the trial protocol showed no advantage of celecoxib (8). Thus, millions of patients were treated with celecoxib in the belief that they would get less serious harms from ulcers, which was not true, and without knowing that they would increase their risk of dying from a myocardial infarction. EMEAs argument is therefore entirely unreasonable.

EMEA also believes that EMEA’s assessment reports are sufficient for our research and notes an initiative that in the future should give the public access to many of EMEA’s documents. We welcome any initiatives that lead to transparency, but that would not be a sufficient substitute for the clinical study reports and the trial protocols. We have previously showed that the EPARs lack important details of the methodology of trials and it is clear that they are insufficient for researchers wishing to perform reliable reviews of the clinical trial evidence. We have identified the published reports of the 7 main clinical studies on orlistat in the application for marketing approval submitted to EMEA and FDA: BM14119B (10), NM14302 (11), NM14161 (12), BM14149 (13), NM14185 (14), BM14119C (15) and NM14336 (16). And we have noted that there are differences between the published versions and the corresponding summaries published by EMEA (17) and FDA (18). For

example, the total number of patients in the analyses of the primary efficacy criteria were 3372 in published papers, 3314 in FDA's statistical review and 2680 in the scientific discussion section of EMEA's EPAR.

In the letter to the Ombudsman from 7 April 2009, EMEA has clarified the relevance of Article 39 (1) and (3) of the TRIPs agreement, and they consider it as a *lex specialis* with respect to Article 3 (2) (a) of the EMEA rules for implementation of Regulation 1049/2001, based on the communication from the European Communities and their Member States on "The relationship between the provisions of the TRIPs agreement and access to medicines" to TRIPs council from 12 June 2001 (IP/C/W/280).

Article 39 (3) of the TRIPs agreement reads as follows: "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use".

The article, however does not define the terms "new chemical entity", "unfair commercial use" and "undisclosed test or other data" – which allows flexibility in its interpretation.

EMEA informed the Ombudsman on 7 April 2009 that the communication from the EC to TRIPs council (IP/C/W/280) highlights that: "The view taken by the EC and their member States is that the Agreement does contain an obligation to protect test data against 'unfair commercial use'". However, EMEA omitted to mention that the communication also says: "and the most effective way of doing so is to deny the regulatory authorities the possibility of relying on such data for a reasonable period of time." The communication does not give a general definition of unfair commercial use, but only describes it in the context when EMEA reviews an application for marketing approval of a new generic version of an already approved medicine. Therefore, EMEAs concerns cannot be regarded as a *lex specialis* in relation to our request that does not involve new generic versions of already existing drugs.

In both letters from 26 February and 7 April to the Ombudsman, EMEA comments the volume of the requested documents. EMEA has stated that the documents comprise 300.000 – 400.000 pages, and that it will be a long and complex work to redact the documents.

We do not agree. We only ask for protocols and clinical study reports and not entire applications including raw data for each randomised patient. In our experience, the bulk of the clinical study reports, with tables of the efficacy and adverse effects, do not comprise more than a few hundred pages for each report. Furthermore, we are only interested in placebo controlled trials. The Danish Drug Agency has granted us access to these reports for a third anti-obesity drug, sibutramin, and, contrary to EMEA, the agency does not see the amount of pages as a problem (we have been told that there are about 20,000 pages in total, or vastly less than what EMEA has estimated for a drug, and many of these 20,000 pages would be irrelevant for us, as we are interested in the bulk of the reports).

Finally, the clinical study reports are finely structured, which can be seen in the guidance EMEA distributes to the companies (available in EMEAs letter to the Ombudsmand 28 April 2008), and it therefore cannot be "a long and complex work to redact the documents", as EMEA claims. It should be a very quick and easy task.

We firmly believe that we should be granted access to the requested documents because:

1) EMEA has consistently failed to provide any evidence that these documents contain any information that is commercially confidential;

2) It will benefit the patients, without whose altruistic willingness to participate in clinical trials, trials would not be possible. The Helsinki Declaration says in article 30: "Authors have a duty to make publicly available the results of their research on human subjects". By its unwillingness to share also the unpublished data with us, EMEA violates The Helsinki Declaration, which is about universal human rights, and, furthermore, EMEA is complicit in the exploitation of patients for commercial gains, as the patients are used as a means to an end, and treated suboptimally as well, which are both unacceptable. The Helsinki Declaration says in article 12: "Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information". If the knowledge base is incomplete, patients will suffer and die unnecessarily, as researchers and companies performing research on similar compounds as one that has been proved to be harmful, will not know about this fact.

Yours sincerely,

Peter C Gøtzsche
Anders W Jørgensen

1. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286:954-9.

2. Berenson A. Evidence in Vioxx suits shows intervention by Merck officials. The New York Times 2005, April 24. http://nytimes.com/2005/04/24/business/24drug.html. Accessed 4 Oct 2007.

3. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis,". N Engl J Med 2005;353:2813-4.

4. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. N Engl J Med 2006. 10.1056/NEJMe068054. Accessed 23 Feb 2006.

5. Topol EJ. Failing the public health - rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9.

6. Lenzer J. FDA is incapable of protecting US "against another Vioxx". BMJ 2004; 329(7477):1253.

7. Harris G. Pfizer says internal studies show no Celebrex risks. New York Times 2005, 5 Febr, Business section. Accessed 7 Febr 2005.

8. Hrachovec JB. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. JAMA 2001;286:2398.

9. Jüni P, Rutjes AW, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? BMJ 2002;324:1287-8.

10. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. Int J Obes Relat Metab Disord 2000 Mar;24:306-13.

11. Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, Zavoral JH, Aronne LJ. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. Am J Clin Nutr 1999;69:1108-16.

12. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. Arch Fam Med 2000;9:160-7.

13. Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. Obes Res 2000;8:49-61.

14. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, Heimburger DC, Lucas CP, Robbins DC, Chung J, Heymsfield SB. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA.1999;281:235-42.

15. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998;352:167-72.

16. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, Lucas CP, Lodewick PA, Canovatchel W, Chung J, Hauptman J. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998;21:1288-94.

17. EMEA. EPAR on Xenical. Scientific discussion. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Xenical/106698en6.pdf

18. FDA. Xenical. Statistical review part 1 to 4. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a.cfm