Getting access to unpublished clinical trials at the European Medicines Agency

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This report is about getting access to the clinical study reports and their corresponding trial protocols, which the drug companies had submitted as a condition for acquiring marketing approval in the European Union for two anti-obesity drugs, rimonabant and orlistat.

All documents in our case, which run to 133 pages, are available on our website, http://www.cochrane.dk/research/EMA.

We have also published a short paper that discusses the main arguments in our case, in the British Medical Journal:

Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011; 342:d2686.

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Despite the existence of hundreds of thousands of randomised trials, doctors are unable to select the best treatments for their patients. This is one of the biggest ethical problems in health care, and the main reason is that research results are being reported selectively. The effect of antidepressants, for example, was 32% larger in the published trials than in all trials that had been submitted to the US Food and Drug Administration (1). This is a large difference, compared to the relatively small effect these drugs have in most patients (2).

Another review of antidepressants showed that the statistical analyses in published reports were considerably more favourable for the drugs than those analyses that are required by law to be submitted to the Drug Agency in Sweden (3). The published analyses are mainly "per protocol analyses" whereas those required by law are "intention to treat analyses," which are far more reliable. It has also been documented that drug companies have concealed suicidal thoughts in adolescents caused by these drugs by relabelling them "emotional lability," or by listing them as admissions to hospital or as dropped out patients without explaining what the problem was (4,5).

Similar examples abound in all therapeutic areas, and even for those trials that eventually do get published, systematic reviews that have compared trial protocols with published reports have shown that trial outcomes are reported quite selectively (6,7).

We would be much better off if all results of all trials became publicly known. In principle, it should be easy to get there, as we have an ethical obligation towards the patients volunteering for the trials that the results become known; otherwise, the patients will have been exploited for commercial or career gains. However, the secrecy in clinical research is substantial. Academic investigators feel ownership to the data, and the drug industry often writes explicitly in its protocols that it owns the data and uses this ownership to actively suppress publication of unwelcome results.

We could get much more reliable overviews of the benefits and harms of drugs if researchers could get access to the tens of thousands of unpublished trial reports at drug agencies. These reports are very detailed, with many analyses and tables, and they therefore also provide more reliable information than published reports of the same trials (3).

It has been virtually impossible to get access to such data at the European Medicines Agency (EMA, previously named EMEA) in London. We describe here how we succeeded to break a hole in the wall after three years of tenacious struggle. We didn't think we would succeed, but the case has set a very important precedent. It should now be much easier for others to get access.

The case

The effect of anti-obesity pills on weight loss is small, even as judged from those trials that have been published (8), and they are generally pretty dangerous as well. People have died from cardiac and pulmonary complications (9), or have experienced psychiatric disturbances such as suicidal events and ideation (10), and several pills have been taken off the market in recent years for these reasons, e.g. Fen-phen, rimonabant and sibutramine.

We found it likely that the effect would be even smaller, and the harms greater, in those placebo-controlled trials that, unknown to the public, collected dust on the shelves of the drug agencies. On 29 June 2007, we therefore applied for access to the clinical study reports that drug companies had submitted as a condition for acquiring marketing approval in the European Union for such drugs, and their corresponding trial protocols. We later narrowed our request to reports on rimonabant and orlistat.

In our letter to EMA, we outlined the plans for our research. For the placebo-controlled trials of anti-obesity drugs, we aimed to explore the robustness of the results by using various imputations for the many missing values in these trials (e.g. first observation carried forward, last observation carried forward, completers analyses, per-protocol analyses and multiple imputation). We had

access to individual patient data from some anti-obesity trials that we had obtained from the clinical investigator, and which would facilitate such imputations. We also wanted to compare unpublished results with published ones and with trial protocols, to check for possible publication bias and outcome reporting bias.

Our arguments were strong. Because of the likely widespread use in future of these drugs, and the pervasive and serious bias in the published literature, we believed the societal interests in getting access to these data should overrule the exemptions in national Freedom of Information Acts. We argued that secrecy was clearly not in the best interest of the patients and that we had previously reviewed a large number of trial protocols of industry-initiated trials, approved by the Scientific-Ethical Committees in Copenhagen, and had not found anything that, with any reasonable justification, could be regarded as confidential to such a degree that it should preclude independent researchers from getting access to the protocols.

Two months later, on 20 August 2007, EMA informed us in a few sentences without any discussion of our arguments that the documents we requested came under "the systems of exceptions set out in the implementation rules, and therefore cannot be released," and specified that the exception referred to commercial interests. We were allowed to appeal this decision to EMA's executive director Thomas Lönngren, which we did four days later, with additional arguments.

We had obtained various EU documents and tried to understand the legal issues. It was clear that the basic rule was to allow the citizens "the widest possible access to the documents the Agency produces or receives and has in its possession" (11). We also learned that EMA would refuse access to a document where disclosure would undermine the protection of commercial interests of a natural or legal person, including intellectual property, unless there is an overriding public interest in disclosure (11).

A basic principle in the European Union is to allow its citizens the widest possible access to the documents its agencies possess. According to the regulations,

"Any citizen of the Union, and any natural or legal person residing or having its registered office in a Member State, has a right of access to documents of the institutions, subject to the principles, conditions and limits defined in this Regulation," and

"Openness enables citizens to participate more closely in the decision-making process and guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen in a democratic system. Openness contributes to strengthening the principles of democracy and respect for fundamental rights as laid down in Article 6 of the EU Treaty and in the Charter of Fundamental Rights of the European Union" (12).

We noted that in our case, the citizens were primarily patients, doctors and taxpayers, and that we found it unacceptable and unethical that only flawed results were available to the public, compared to the results that were known to the drug regulatory agencies.

We noted that the Vioxx case had demonstrated that the withholding of unfavourable results from the public domain can have lethal consequences for the patients, and that doctors would inevitably sometimes harm their patients unknowingly because of the selective reporting, which seems to be the rule, rather than the exception for drug trials (3,5,6). We repeated that none of the 102 trial protocols we had reviewed earlier, half of which were supported by the drug industry, disclosed anything that could undermine the protection of commercial interests of a natural or legal person, including intellectual property, and that apparently, the Scientific-Ethical Committees in Copenhagen had either come to the same conclusion or had concluded that there was an overriding public interest in our research.

We noted it was particularly unlikely that clinical study reports should contain anything that could undermine the protection of commercial interests, as one would not expect to find details of patented production processes, for example, in these reports.

We also noted that the lack of openness and transparency in EMA violated basic principles in the EU Treaty and must be changed, as it was also unethical.

Finally, we noted that we expected that Lönngren's reply to our appeal would not merely refer to EU regulations, but would address, point by point, our documented concerns about secrecy in drug regulation and our arguments in favour of freedom of access. In case of continued denial of access to the requested documents, we also asked EMA to explain with what reasoning EMA considered that the commercial interests of the drug industry should override the welfare of the patients, as this attitude will increase 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.

A month later, Lönngren sent a one-page letter where it seemed he had merely copied and pasted the information in the first letter. He also noted that EMA took actions where appropriate to protect public health and that we could find European Public Assessment Reports (EPARs) on EMA's website. Lönngren treated us as if we had been patients or practising doctors, but we had clearly explained in our first letter that we were scientists. He must have known that these summaries are completely worthless for scientists and for the science we had planned and had described in our letter, and he furthermore did not address our arguments, as we had requested. He told us we could lodge a complaint to the European Ombudsman or institute court proceedings against the Agency.

Appeal to the European Ombudsman 8 Oct 2007

We appealed to the European Ombudsman, P. Nikiforos Diamandouros, on 8 Oct 2007 and sharpened our arguments about why concerns for the patients' welfare should be given priority over concerns for the drug industry's commercial interests.

We noted that Vioxx had likely caused about 100,000 unnecessary heart attacks in the USA alone (13) (which corresponds to about 10,000 unnecessary deaths) and that Merck, the maker of the drug, had concealed this harm for several years. Furthermore, that is had been shown, by comparing published trial reports with documents submitted to the Food and Drug Administration in the USA (FDA) on the same trials that several cases of sudden cardiac deaths and of non-fatal myocardial infarction on Merck's drug were omitted from the published trial reports (14-18). An editorial in The Lancet concluded: ”with Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest” (19).

We gave other examples where 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 the flaws in the published literature. For example, a pivotal trial report on another anti-arthritis drug, celecoxib, reported misleading short-term data in violation with the trial protocol (20). 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 (21).

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 (22,23).

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 lability” (5,6). 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 randomised to the placebo (24,25). 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 (26).

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” (27).

We noted that we were aware that EMA publishes the outcome of the scientific discussions on the various drugs (EPARs) on its website, but that these short summaries are not sufficient for an independent evaluation of the trials that have been submitted to EMA. 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.

We also took issue with Lönngren’s statements about EMA as a guardian of public health. Lönngren had stated that EMA monitors the efficacy and safety of all medicines, but we argued, with reference to our examples above, that this was clearly not sufficient. Monitoring 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 such 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 randomised clinical trials where the control group does not receive the drug in question.

We found the two letters from EMA wholly unconvincing and therefore appealed to the European Ombudsman that it should not be accepted that EMA prioritises to protect the commercial interests of the drug companies, rather than protecting the lives and welfare of the patients.

We argued that the secrecy in drug regulation that EMA 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 were applying for would, as a general principle, not be anti-competitive, as all companies would 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 depend largely on public resources, the public should have access to data of interest” (28). We added 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 to them.

Finally, we asked 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 a 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" (28).

On 25 Oct 2007, the Ombudsman wrote to us that he had asked EMA to address our complaints, which he summarised:

1. "EMEA has given insufficient reasons for its decision, in particular as regards the existence of a public interest in disclosure overriding commercial interests."

2. "EMEA's decision to deny access based on the protection of commercial interests is unconvincing, given in particular that the study reports and protocols requested do not appear to indicate any commercial interest."

EMA's reply to the Ombudsman 30 Jan 2008

The Ombudsman had given EMA a three months deadline, till 31 January, and Lönngren didn't reply before 30 January 2008, one day before the deadline. He sent a 3-page letter and an official EMA document (11).

Lönngren argued that "the disclosure would undermine the protection of commercial interests of a natural or legal person, including intellectual property," and referred to the EU regulations (12) and to "Rules for the implementation of Regulation (EC) No 1049/2001on access to EMA documents"(11), which he attached. But he still didn't explain why he felt our request for access would undermine the protection of commercial interests.

Lönngren also referred to Article 39.3 of the WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), which "imposes on the Members a specific obligation of protection of undisclosed information, with particular reference to undisclosed test or other data submitted to Members in order to obtain marketing approval for pharmaceutical products, which must be protected against unfair commercial use. In this respect, Members have also to protect such data against disclosure, except where necessary to protect the public."

Lönngren used TRIPs in his argumentation: "In this regard, it is worth to recall that commercially confidential information has to be considered any trade secret or commercial confidence and, more in general, any kind of information which disclosure would undermine the interest or, in other words, prejudice to an unreasonable degree, the commercial interests of individuals or companies concerned."

He noted that, "Although the complainants have alleged several motivations for supporting the existence of a public interest in disclosure, the public interest of publishing these data has to be balanced against the interest of protecting a third party (the applying company) that, in case of improper disclosure of the content of the concerned documents, would be adversely affected."

Lönngren acknowledged that if there was "*an overriding public interest in disclosure,*" the documents should be disclosed. He also cited our argument from our first letter to EMA, that additional analyses were needed before the patients and their doctors could obtain a balanced view of the benefits and harms of anti-obesity drugs.

However, he again completed ignored that our request was related to our explicit plan for doing concrete research based on the requested documents. We perceived his subsequent arguments as irrelevant. Lönngren mentioned that it was "important to note that Article 57(1) (m) of Regulation (EC) No 726/2004 expressly gives the EMA the task of informing healthcare professionals and patients on information relating to medicinal products that are approved or rejected by the Community. In addition to specific prescribing information for healthcare professionals ('summary of product characteristics') and specially written information for patients

('package leaflet') in all EU official languages, the EMA systematically publishes its scientific assessment of the benefits and risks of all centrally approved medicines. In each instance, the benefits and risks of the medicine are explained and balanced against each other."

We had already carefully explained that this publicly available information was insufficient for our planned research, but Lönngren provided additional irrelevant arguments:

"The assessment of balance and risks is an obligation of the Agency. This balance of benefit and risk may change over time as experience is gained with a medicinal product. Working together with the national competent authorities, the EMA constantly monitors this balance and updates the assessment report and product information as appropriate. With this regard and on balance with the allegations of the complainants, the Agency cannot identify any overriding public interest that could justify the disclosure of the concerned documents."

Finally, Lönngren noted that, "Notwithstanding the above, the Agency acknowledges that transparency is considered as a key value in the public health policy throughout Europe. For this reason, it is my intention to shortly launch a public consultation with all the Agency's stakeholders with the aim to further improve the Agency's openness approach with regard to access to documents and proactive disclosure of information on quality, safety and efficacy of medicinal products."

We had some difficulty accepting that EMA aimed "to further improve the Agency's openness approach." How may one improve on something that doesn't exist? There was absolutely no "openness approach" at EMA, but firmly closed doors.

Our reply to the Ombudsman 26 Feb 2008

In his letter to EMA, the Ombudsman had noted that, "EMA has given insufficient reasons for its decision, in particular as regards the existence of a public interest in disclosure overriding commercial interests."

We felt that EMA's arguments were now of a type that could equally well have been written by the CEO of a major drug company. This could actually have been the case, as drug agencies consult widely with drug companies, including which wording they should use, and they have often been accused of being on too friendly terms with the companies it is their duty to regulate. It was all about protecting companies, not about protecting patients. We didn't air our concerns to the Ombudsman, however, but merely summarised EMA's reasoning about commercial interests:

- Allowing us access would undermine the protection of commercial interests.
- Access to undisclosed data must be protected against unfair commercial use.
- Disclosure of commercially confidential information could prejudice to an unreasonable degree the commercial interests of companies.
- The public interest in allowing us access has to be balanced against the interest in protecting the applying company that, in case of improper disclosure, would be adversely affected.
- EMA publishes its scientific assessment of the benefits and risks of all centrally approved medicines.
- EMA shall refuse access unless there is an overriding public interest in disclosure.

We referred to the documentation we had cited in our previous letter and repeated why EMA's position would likely have the following consequences:

- Patients will die unnecessarily, sometimes by the thousands, because of the treatments their doctors prescribe to them out of ignorance about what the true balance is between the benefits and harms.
- Millions of patients in the European Union will be treated with inferior, and sometimes harmful drugs, which also involves a huge waste of limited resources. The fact that EMA publishes its scientific assessments of the benefits and risks of all centrally approved medicines cannot prevent this from happening, as these documents do not contain all the information researchers need in order to provide reliable systematic reviews about the benefits and harms of drugs that enable clinicians and patients to make rational, and fully informed, decisions about drugs.

In his letter to EMA, the Ombudsman had also noted that, "EMA's decision to deny access based on the protection of commercial interests is unconvincing, given in particular that the study reports and protocols requested do not appear to indicate any commercial interest."

We pointed out to the Ombudsman that we had explicitly requested that EMA should state its reasons why EMA felt commercial interests should override concerns for the welfare of the patients. Furthermore, we remarked that EMA had still failed to explain in what way allowing us access to clinical study reports and corresponding trial protocols would undermine the protection of commercial interests; how it could lead to unfair commercial use; and why commercial interests should override concerns for the welfare of the patients.

We repeated that we were scientists and needed the information in order to be able to provide doctors and patients with reliable information about the benefits and harms of anti-obesity drugs. We furthermore explained that doctors get information about drugs by reading reports and reviews of randomised clinical trials in medical journals that, on average, are seriously flawed, compared with all the trial reports that have been submitted to EMA in applications for marketing authorization. We noted that a systematic review from 2008 from USA, where the researchers had access to data at the Food and Drug Administration (FDA), confirmed this. The effect of antidepressant drugs was exaggerated by 32%, on average, in the published literature, compared to all the data available at the FDA (1). Another systematic review, also based on FDA data, published the same day we sent our letter to the Ombudsman, 26 February 2008, found that antidepressant drugs have virtually no effect, apart from the most severe cases of depression (29).

We argued that the use of antidepressant drugs is so widespread that it meant that millions of citizens in the European Union were currently being treated unnecessarily, and we concluded that EMA prioritises to protect the profits of drug companies rather than protecting the lives and welfare of patients, as both cannot be protected at the same time. We found this particularly worrying for anti-obesity drugs, as these drugs have little effect, even when considering only the published data, and as they have serious harms. It is therefore highly likely that the balance between their benefits and harms would look different, if unpublished data were included in systematic reviews of the drugs.

We also noted that the study from USA on antidepressants (1) illustrated that there is far more openness and better access to data at the FDA than at EMA, and that the extreme secrecy in European drug regulation needed to be changed.

We mentioned that changes were already happening, e.g. a European register of drug trials in children would be established, and the results submitted to the regulatory agency would be made public (30). The article describing this said that, "This transparency is essential, as a database of paediatric clinical trials only accessible to the European Medicines Agency would not benefit children in Europe". We argued that the European Commission's Directorate General for Research

was taking steps to improve access (31,32), just as it had happened for trials sponsored by the Medical Research Council in UK and by the National Institutes of Health in USA (31).

We reiterated that EMA's attitude was ethically indefensible, as the prime duty of drug agencies is to protect patients from unnecessary harm. Disclosing the type of data we were applying for would, as a general principle, not be anti-competitive, as all companies would be affected equally by it. But it would lead to more transparency, more rational use of resources, and less harm.

We also reiterated that the Ombudsman should consider particularly carefully that drug regulatory agencies have a conflict of interest when they deny others access to the data in their possession. When doing so, the agencies cannot be questioned over their decisions, or over the quality of the short summaries they make available to the public.

The Ombudsman describes his request for clarification from EMA 18 March 2008

After having considered the responses from EMA and us, the Ombudsman asked EMA for further clarification.

EMA should specify why clinical study reports and corresponding trial protocols were to be considered as covered by commercial interests and in how far their disclosure for scientific purposes would be liable to undermine the protection of commercial interests.

The second issue concerned TRIPs, which allows contracting parties to grant access to data submitted in the process of marketing approval, provided that steps are taken to ensure that the data are protected against unfair commercial use. The Ombudsman mentioned a case he had previously dealt with, about a complaint relating to refusal of access to an audit report. In that case, the European Investment Bank, apart from granting public access to certain excerpts of the report, undertook to grant the complainant private access to certain further sections. The Ombudsman asked EMA to consider a similar approach in our case.

EMA replies to the Ombudsman 28 April 2008

The Ombudsman gave EMA a deadline at 30 April, and Thomas Lönngren replied two days before the deadline.

In relation to "protecting commercial confidential information," Lönngren sent a 48-page template for the structure and content of clinical study reports and explained that, "these reports are extremely detailed and extensive." He furthermore noted that the dossier of the reports represented "the full detail of the clinical development programme for a medicinal product," and that it constituted "the most substantial part of the applicants investment (in both elapsed time and cost) in developing a product up to the point of the MAA [Marketing Authorisation Application]."

The Ombudsman had asked EMA to specify why clinical study reports and corresponding trial protocols were to be considered covered by commercial interests and in how far their disclosure for scientific purposes would be liable to undermine the protection of commercial interests. In our opinion, Lönngren didn't specify this.

With respect to the Ombudsman's second request for clarification, Lönngren cited from WTO's TRIPs Agreement: *"Members, when requiring, as a condition of approving the marketing of pharmaceutical (…) products, the submission of undisclosed test or data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use."* He furthermore argued:

"This is the only provision enforceable in the EU legal system, and therefore also binding the EMA as such, which expressly foresees a specific legal obligation to protect undisclosed data in the particular framework of the procedure for the approval of medicinal products. For this reason it is

regarded as a *lex specialis* in respect to Article 3 (2) (a) EMA rules for implementation of Regulation 1049/2001. This Article foresees a general exception to the principle of transparency whenever the disclosure of a document would undermine the protection of commercial interests, without specifying the framework of applicability." Lönngren then dismissed the possibility to follow the example of the European Investment Bank with the argument that the Investment Bank had adopted its own public disclosure policy, which differed from Regulation (EC) 1049/2201.

Lönngren also introduced a new barrier for gaining access, one of practicality. He said that the documents we requested contained:

"substantial amounts of personal data, hence the need for reduction [sic] of the concerned document before disclosure. The redaction, in the view of allowing a partial disclosure of the document, would involve long and complex work which would cause the Agency a disproportionate effort in terms of time and resources, that would be inevitably devoted to this exercise and would divert attention from the core business activities as foreseen by Article 57 Regulation (EC) 726/2004. As a specific example, is of note that the clinical study reports and protocols for the requested placebo-controlled trials of rimonabant comprise more than 500 volumes of documentation (approximately 300-400 pages per volume) corresponding to 29 studies. It is worth mentioning that this amount of information only refers to data submitted as a support for the initial marketing authorisation."

He continued:

"I would also like to take the opportunity to counter argue the observations raised by the complainants in their letter to the Ombudsman dated 28 February 2008 with particular reference to the fact that *"scientists need this information to provide doctors and patients with reliable information about benefits and the harms of the anti-obesity drugs."*

"It's worth reiterating the fact that it is expressly in the EMA's remit to inform healthcare professionals and patients on data relating to medicinal products that are approved or rejected by the Community. The Agency undertakes this obligation through the provision of independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public health that involve medicines, as foreseen by Articles 57(1) (m) and 80 of Regulation (EC) No 726/2004. As already mentioned in our letter to the Ombudsman dated 30 January 2008, the evaluation of balance and risks of medicines is an obligation of the Agency. The network established with the national competent authorities of EU and EEA Member States, allows the EMA to constantly supervise this balance and update the assessment report and product information accordingly, in view of its continuous provision of information to patients, healthcare professionals and general public."

Lönngren furthermore argued:

"All the requests for access to documents are therefore handled in accordance with the rules for implementation of Regulation 1049/2001, which foresee, as a general principle, to grant access to all applicants irrespective of the reasons and motivations provided (which the applicant is not even obliged to state) and, on the contrary, to deny access in all the exceptional cases as foreseen by Art 3. The EMA Implementing Rules on access to documents do not foresee instead the possibility of granting access to certain categories of applicants on the basis of their motivation and to enter into a single confidentially agreement with the applicant."

What we didn't write in our reply to the Ombudsman on 17 June 2008 was that the scientists who give advice to EMA and other drug agencies are not "independent" but usually have conflicts of interest in relation to the drug industry, and that there are numerous examples that the FDA isn't capable of protecting the public against the harms of drugs, not even lethal harms.

Our reply to the Ombudsman 17 June 2008

In our reply to the Ombudsman, we noted that we had previously described that considerable details of the methodology of trials were needed to perform reliable systematic reviews about benefit and harms of drugs:

"Such information is rarely available, neither in medical journals, nor in EMA's scientific assessment reports. As an example of lack of details, EMA's assessment report on Xenical (orlistat) does not mention anything about allocation concealment. The report on Acomplia (rimonabant) presents data from 49 trials, 8 of which are phase III trials that are relevant for us, but allocation concealment is only described for 4 of these. Details on concealment of allocation are very important. Inappropriate or unclear concealment of allocation introduces bias and overestimates the effect by 18% on average." (33).

We noted that EMA had emphasised the degree of detail of the clinical study reports by referring to their guide on structure and content of them, and, as this guide described general and well-known principles for drug trials, it did not indicate that clinical study reports contain commercially confidential information, in contrast to EMA's conclusion.

We also argued that although clinical trials require considerable resources, this only represents a minor part of the pharmaceutical industry's total expenses, e.g. in USA, the pharmaceutical industry spends about twice as much on drug promotion than on research and development (34). Furthermore, we found EMA's argument irrelevant for our request of access to data:

"In fact, we believe that if commercial success is dependent on withholding data that are important for rational decision-making for doctors and patients, then there is something fundamentally wrong with our priorities in health care."

We also took issue with EMA's argument related to practicality and confidentiality related to tables with individual patient data. We argued that Article 6 states that if only parts of the requested document are covered by any exceptions, the remaining parts of the documents shall be released. We also noted that EMA's guide on structure and content of clinical study reports indicated that removing information on individual patient data should be rather easy, in contrast to EMA's assertion that it would be "a long and complex work."

Finally, we noted that, according to Regulation (EC) No 1901/2006 article 41.2, details of all paediatric trials submitted to EMA would be made public by the Agency, and that it would seem difficult, if not impossible, to defend a position that only details on trials in children and not those of trials in adults would be made publicly available.

We summarised our opinion thus:

"EMA has again failed to specify why clinical study reports and protocols are to be considered as covered by commercial interests," and

"Disclosure of the requested documents will benefit the members of the European Community and people in the rest of the world, as they would get a more reliable picture of the benefits and harms of drugs used against obesity. This is important for rational decision-making, and we therefore firmly believe that the interests of the patients should override the commercial interests of the companies marketing anti-obesity drugs."

The Ombudsman proposes a friendly solution to EMA 22 January 2009

During the next six months, no further documents were sent to us. In January 2009, the Ombudsman proposed a friendly solution, in accordance with Article 3(5) of the Statute of the European Ombudsman. The Ombudsman criticised EMA and made the preliminary finding that

EMA did not provide sufficient reasons for its refusal to grant access to the documents requested, and that failure to do so amounted to an instance of maladministration. The Ombudsman's proposal was:

"EMA could reconsider the complainants' request for access and grant access to the documents concerned, or provide a convincing explanation as to why no such access can be granted."

The Ombudsman summarised our case over 12 pages, with 38 numbered items, and the most important issues were:

"The complainants stressed that it was essential that the clinical study reports and corresponding trial protocols be made available for additional analysis by independent researchers, given that empirical studies suggested that biased reporting on drugs trials was common."

"They stated that it was unlikely that clinical study reports would contain anything that could undermine the protection of a natural or legal person's commercial interests. They also asked EMA to explain, if it were to uphold its initial decision, why it considered that commercial interests of the drug industry should override the welfare of patients."

"In their observations, the complainants submitted that, as a likely consequence of EMA's position, patients would die unnecessarily and would be treated with inferior and potentially harmful drugs."

"Pursuant to Article 18 of the European Code of Good Administrative Behaviour, every decision taken by an institution *"shall state […] clearly […] the legal basis of the decision"*. Against this background of EMA's decisions, as well as the comments it made in the course of the inquiry, the Ombudsman considers that the legal basis on the basis of which EMA refused access is not clear. Consequently, the Ombudsman makes the preliminary finding that EMA did not provide sufficient reasons for its refusal to grant access to the documents requested, and that failure to do so amounted to an instance of maladministration."

"According to Article 1(1) of the Rules, their aim is to ensure the widest possible access to the documents EMA produces or receives and has in its possesion. It follows that Article 39(3) of the TRIPs agreement and the Rules appear to pursue different aims."

"Moreover, Article 39(3) of the TRIPs agreement refers to the protection of data submitted in the framework of marketing approval *"against unfair commercial use"*. Thus, it appears that, leaving aside the issue of protecting the public, the response to whether access can be granted pursuant to this provision hinges on the future use of disclosed data or the availability of steps to prevent certain future use. On the other hand, the Rules as such are indifferent to the use of disclosed documents; instead they are predicated on a general obligation to grant access. Thus, the purpose of Regulation 1049/2001 and the Rules is to give the general public a right of access to documents.[4] At first sight, it is therefore difficult to reconcile an access regime, which takes into account the future use of disclosed data, with the Rules."

"In its decisions on both the complainants' initial and confirmatory applications, EMA relied on Article 3(2)(a) of the Rules, which read as follows:

"The Agency shall refuse access to a document where disclosure would undermine the protection of:

a) commercial interests of a natural or legal person, including intellectual property, […] unless there is an overriding public interest in disclosure"."

"According to Article 1(1) of the Rules, their aim is to ensure the widest possible access to the documents EMA produces or receives and has in its possession. It emerges from the settled case-law of the Community courts regarding Regulation 1049/2001 that the exceptions to the general right of access to documents must be interpreted and applied strictly.[7] The mere fact that a document concerns an interest protected by an exception cannot itself justify the application of that

exception. Therefore, before lawfully relying on an exception, the institution concerned is required to assess (i) whether access to the document would specifically and actually undermine the protected interest and (ii) whether there is no overriding public interest in disclosure. That assessment must be apparent from the reasons underpinning the decision[8]."

"... it is not apparent from EMA's reasoning why, in its view, access to the documents requested would specifically and actually undermine commercially interests."

"The Ombudsman considers that commercial interests may be at stake. However, bearing in mind that exceptions to the right of access to documents are to be interpreted narrowly and taking the explanations given by EMA into account, he fails to see how granting access would *specifically and actually undermine* commercial interests, thereby meeting the condition set by the case law of the Community courts. It appears useful to add that the risk of an interest being undermined must, in order to be capable of being relied on, be reasonably foreseeable and not purely hypothetical.[9]"

"Even if commercial interests were specifically and actually undermined by disclosure, access still has to be granted if there is an overriding public interest in disclosure. Turning therefore to the existence of an overriding public interest, the Ombudsman notes that, according to the case-law of the Community courts regarding Regulation 1049/2001, the institution concerned needs to balance the particular interest to be protected by non-disclosure against, *inter alia*, the public interest in the document being made accessible. This balancing of interests must take into account the advantages stemming from increased openness enabling citizens to participate more closely in the decision-making process and guaranteeing that the administration enjoys greater legitimacy and is more effective and accountable to the citizen in a democratic system.[10] Furthermore, the overriding public interest capable of justifying disclosure need not be distinct from the principles underlying Regulation 1049/2001.[11]"

"The complainants raised a number of concerns regarding patients' health, which would establish an overriding public interest. The Ombudsman considers that, in order to establish an overriding public interest in disclosure, plausible and sufficiently concrete arguments suggesting the existence of such interest have to be submitted. At the same time, he recalls that the question regarding the existence of an overriding public interest only has be to answered once it has been shown that commercial interests would be specifically and actually undermined by disclosure. Given that the Ombudsman finds this not to be the case, at this stage, he does not yet need to take a definitive stance on whether or not an overriding public interest exists."

The Ombudsman furthermore noted, with reference to a concrete case from the Court of First Instance, that institutions must "retain the right, in particular cases where concrete, individual examination of the documents would entail an unreasonable amount of administrative work, to balance the interest in public access to the documents against the burden of work so caused, in order to safeguard, in those particular cases, the interests of good administration." He added, however, that this possibility remained applicable only in exceptional cases, where "the administrative burden entailed by a concrete, individual examination of the documents proves to be particularly heavy, thereby exceeding the limits of what may reasonably be required."

"The Ombudsman accepts that the amount of information covered by the complainants' request for access could, in principle, entitle EMA to rely on the derogation from a concrete and individual examination of the documents. However, he also recalls that the complainants have convincingly argued that EMA overestimated the administrative burden involved. They pointed out that, in view of the structured nature of clinical study reports, which separate individual patient data from other sections of the reports, removing private data should be relatively easy. Against this background, and bearing in mind the exceptional nature of the derogation developed in the case-law of the Court of First Instance, the Ombudsman considers that EMA insufficiently explained why editing the documents would entail an excessive administrative burden on it."

About the TRIPs agreement, the Ombudsman considered that disclosure was not prohibited, if data disclosed could be protected against unfair commercial use.

"The Ombudsman recalls that the complainants repeatedly underlined, both in their applications to EMA, as well as in the course of his inquiry, that their request for access was motivated by purely scientific concerns. In complaint 1776/2005/GG, the European Investment Bank (EIB) granted the complainant in that case private access to certain sections of an audit report which could not be publicly disclosed. In that case, the Ombudsman emphasised that he very much appreciated the EIB's constructive and co-operative approach. He also stated that the innovative way in which the EIB complied with the complainant's request for access, whilst at the same time protecting the legitimate interests of third parties, could serve as a model for future cases."

"The approach followed by the EIB lends itself to EMA fulfilling its obligations under Article 39(3) of the TRIPs agreement while respecting, as far as possible, the principle of transparency in the present case. Thus, the Ombudsman considers that granting private access to the complainants, with a view to conducting the scientific study envisaged by them, could reconcile the complainants' interest in getting access with the interest in protecting data against unfair commercial use, in line with Article 39(3) of the TRIPs agreement."

"In its further comments, EMA explained that the Rules do not foresee the possibility to grant access to certain categories of applicants on the basis of their motivation. Nor do they provide a basis for entering into a confidentiality agreement with an applicant. However, in the Ombudsman's view, the fact that the Rules do not foresee the possibility of granting private access cannot exclude the possibility of granting private access on the basis of Article 39(3) of the TRIPs agreement. Against this background, the Ombudsman considers that EMA insufficiently explained why private access cannot be granted."

"In light of the above, the Ombudsman makes the preliminary finding that EMA did not provide sufficient reasons for its refusal to grant access to the documents requested, and that failure to do so amounted to an instance of maladministration."

Reply from EMA to the Ombudsman 26 February 2009

The Ombudsman gave EMA a deadline at 28 February, and Thomas Lönngren replied two days before the deadline.

Lönngren's noted:

"It's worth mentioning that although a sound and clear definition of commercially confidential information (CCI) cannot be found, neither in the legislation nor in the jurisprudence, generally CCI is defined as follows:

Information that could be of benefit for a competitor, the disclosure of which could cause a disproportionate prejudice to and seriously harm the commercial interest of the party. Under the definition of CCI fall the following categories:

a) Intellectual property: Concerns the development and research (very costly in the pharmaceutical sector) prior to the filing of a patent or a design. The disclosure of the information prior to obtaining a patent can prevent it from being registered. Therefore, high interest to put measure in place to keep it secret;

b) Trade secrets: Concern formulas, manufacturing and control processes which are or may be used in trade. They are generally not in the public domain and can draw a certain value from not being known. They are also subject to reasonable efforts of being kept secret;

c) Commercial confidences: Concern every piece of information which does not have a commercial value as such, but its disclosure might provoke damage to the party (e.g. structures and development plans of company, marketing strategies, etc.).

As already explained in our reply dated 28 April 2008, the data contained in those third parties documents have commercial value."

Lönngren then explained what clinical study reports and clinical trial protocols were and noted that, "it would be reasonably foreseeable that the disclosure of this information would specifically undermine the interest of the third party owner of the document. The data contained in the reports and protocols could in fact be used by competitors as a basis to start developing the same or a similar medicinal product on their own, using the information and data for their own economical advantage. And moreover from the data contained therewith, the competitors could gather valuable information on the long term clinical development strategy of the company."

Lönngren furthermore noted:

"The EMA is of the opinion that the link between the sharing of the requested documents and the possibility of saving lives of patients was not satisfactorily proven by the applicant to justify the release of the clinical study reports and corresponding trials protocols. The EMA believes that the underlying meaning of the principle of transparency is to enable citizens to scrutinize the activities of the Agency and strengthening, in this way, the democratic scrutiny and control over its functions."

"To this purpose, the EMA, according to article 80 of Regulation (EC) 726/2004, regularly publishes European public assessment reports and press releases through which the public is informed about EMA's activities and can therefore gather information about the work of the Agency. On the other hand, it is important to underline that, the activity of evaluation on the safety and efficacy of a medicinal product during its whole lifecycle, is still expressively and specifically a task of the Agency, and not a shared responsibility of the general public. Therefore the EMA considered that the motivations put forward by the applicant to try to prove the existence of an overriding public interest in the disclosure of the documents were not sufficient."

"In addition to this, it is worth noting that the EMA has drafted an Access to Documents Policy – currently undergoing public consultation – which foresees the possibility for the public to have access to many documents related to the EMA's activities, with particular reference to the CHMP Assessment Report and to the (Co)- Rapporteur Assessment Reports. In relation to these two categories of documents, the EMA holds the view that the release of the assessment reports for the two medicinal reports at stake, could satisfy the request of the complainants."

"The central position of responsibility of the Agency in the protection of public health is also supported and reinforced by the fact that, firstly with reference to the medicinal product Acomplia (Intellectual Non-proprietary Name "Rimonabat" [sic]), The European Medicines Agency recommended the suspension of the marketing authorisation."

"Secondly, as far as the other medicinal product – Orlistat – is concerned, after evaluating safety and efficacy aspects, on 21 January 2009 the EMA granted approval for the sale without prescription."

"Due to the presence of a great amount of commercially confidential information and personal data, the documents would in fact need to be redacted and could only be partially released. It is also important to say that, as a result of the redaction exercise, the documents will be deprived of all the relevant information and the remaining parts of them will be worthless for the interest of the complainant."

"As already mentioned the clinical study reports protocols are annexes of the dossier submitted by the pharmaceutical companies and in the present case comprise more than 500 volumes of documentation, each of which containing approximately 300-400 pages. Therefore, the redaction of these documents would nevertheless entail a disproportionate effort in term of time and human resources that would be distracted from their core activities. This would mean in practical terms the redaction of 300.000 – 400.000 [sic] pages for the two medicinal products at stake."

"For the above mentioned reasons the EMA believes that also partial access to the documents should be denied since the completion of the request of the applicant would entail a disproportionate effort for the Agency, which would need to distract human resources from their normal activities connected to the core business."

Lönngren concluded that the information we had required:

"cannot be disclosed due to the commercially confidential nature of the information contained and, moreover, that the applicant has not given evidence of the existence of an overriding public interest which could potentially justify the disclosure of the documents. In any case, should the Ombudsman still believe that the documents have to be released, the effort that the redaction of those documents would entail for the Agency in terms of time and human resources would be disproportionate and therefore access should be denied also in this case."

We found this conclusion remarkable. The Ombudsman had requested that EMA justified its position that there wasn't an overriding public interest, but Lönngren tried to avoid to reply by playing the ball back to where it came from by claiming that *we* should not have given evidence of the existence of such an interest. This wasn't correct and it was irrelevant. A suspect in a court case who is asked for his alibi on the day of the crime doesn't get off the hook by asking for someone else's alibi.

It seemed to us that Lönngren tried to hedge his bets so that it just couldn't 'go wrong' and lead to disclosure of the requested documents he didn't want to disclose.

The Ombudsman asks EMA for further clarification 10 March 2009

The argumentation from EMA was obviously deficient and the Ombudsman didn't buy into it, but asked for further clarification:

"In its reply to the Ombudsman's friendly solution proposal, EMA exclusively refers to the commercial interests-exception as the legal basis for its refusal to grant access. However, in its reply of 28 April 2008 to the Ombudsman's request for additional information, EMA considered Article 39(3) of the TRIPs Agreement as constituting a lex specialis. Again in its reply of 28 April 2008, EMA also referred to the great amount of personal data contained in the documents requested which it mentioned again in its reply to the Ombudsman's friendly solution proposal.

(i) Against this background, could EMA please specify which relevance, if any, it considers Art 39(3) of the TRIPs Agreement to have for the present case?

(ii) Could EMA further please specify which relevance, if any, it considers the need to protect the privacy and the integrity of the individual to have for the present case?

(iii) In case EMA considers Article 39(3) of the TRIPs Agreement of relevance to the question of access in the present case, could EMA please comment on the Ombudsman's considerations in paragraphs 36 and 37 of his friendly solution proposal?"

These two paragraphs were about the European Investment Bank granting private access to part of the documentation, which could not be publicly disclosed.

Reply from EMA to the Ombudsman 7 April 2009

The Ombudsman gave EMA a deadline at 15 April, and Thomas Lönngren replied eight days before the deadline. Usually, Lönngren didn't reply before the deadline ran out, but we noted that there were Easter holidays in the period between the 7 and 15 April.

As far as we could see, Lönngren was running out of arguments, as he merely restated what he had already said in his letter.

About the TRIPs agreement, he noted 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’ (document attached for your convenience).”

About private access, he noted that, “once a document is released to a single applicant, it is considered of public domain.” He added:

“The legislation does not foresee a third option of a so called “private access” and therefore granting a private access to some documents would imply entering, every time, into a confidentiality undertaking with the requesters and creating unequal treatment conditions towards different categories of applicants. In view of the fact that this possibility is not indicated by Regulation (EC) 1049/2001 and that considering the number of requests addressed to the Agency, entering a confidentiality agreement with every applicant, would imply a big effort in term [sic] of human resources and workload, the EMA is not considering the proposed solution as a viable one.”

Lönngren also repeated his views on the “substantial amounts of personal data” and the “more than 500 volumes of documentation (approximately 300-400 pages per volume) corresponding to 29 studies,” which meant that, “the redaction of the document, would involve long and complex work which would cause the Agency a disproportionate effort in terms of time and resources.”

Our reply to the Ombudsman 19 May 2009

The Ombudsman asked for our observations and in our reply, we discussed both of EMA’s letters (from 26 February and 7 April 2009).

We rejected EMA’s opinion that competitors could use the clinical study reports and corresponding protocols as a basis for developing the same or a similar medicinal product for their own economic advantage and get valuable information about the company’s long term clinical development strategy. These documents represent the last phase of the development of a drug - the clinical trials in patients - which 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. We therefore found it very hard to believe that the documents could have any use for other companies as a starting point for the development a similar drug. In fact we believe that, compared to the documents that we had 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 - they even see an advantage in doing so as it might attract investors - we believed EMA’s argument had 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 believed EMA was wrong in claiming that the requested documents fall into one or more of the three categories in their definition of commercially confidential information (intellectual property, trade secrets and commercial confidences). First, 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 EMA’s guidelines for clinical study reports 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.

EMA also commented on "*Evidence of an overriding public interest in disclosure,"* and had the opinion that we had not proved that lives would be saved if we got access to the documents. We noted that we of course could not prove this in the concrete case, as we were denied access to the evidence! We repeated that published reports of industry-conducted trials are biased and therefore clearly insufficient for practicing clinicians when they make decisions, and for researchers when performing systematic reviews and meta-analyses of the clinical trial evidence. If doctors only rely on published information, patients will therefore not be treated optimally and some will die unnecessarily. We mentioned again the case of the anti-arthritis drugs, the COX-2 inhibitors.

The drug company Merck concealed cases of myocardial infarction and deaths from rofecoxib, which were missing in reports of the pivotal trials (14,16-18). This misconduct led to the unnecessary deaths of thousands of patients (13,35). New York Times reported that Pfizer denied that celecoxib causes heart attacks at a hearing with the FDA (36), 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 (36). 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 (20,37). 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 (20). Thus, millions of patients were treated with celecoxib in the belief that they would get less serious harms from ulcers, which wasn't true, and without knowing that they would increase their risk of dying from a myocardial infarction. EMA's argument was therefore entirely unreasonable.

EMA also believed that its assessment reports were sufficient for our research and noted an initiative that in the future should give the public access to many of EMA's documents. We welcomed any initiatives that would lead to transparency, but that would not be a sufficient substitute for the clinical study reports and the trial protocols. We had previously shown 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 had identified the published reports of the 7 main clinical studies on orlistat in the application for marketing approval submitted to EMA and FDA: BM14119B (38), NM14302 (39), NM14161 (40), BM14149 (41), NM14185 (42), BM14119C (43) and NM14336 (44). And we had noted that there were differences between the published versions and the corresponding summaries published by EMA (45) and FDA (46). 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 EMA's EPAR.

In its letter to the Ombudsman from 7 April 2009, EMA clarified the relevance of Article 39 (1) and (3) of the TRIPs agreement, and they considered it as a *lex specialis* with respect to Article 3 (2) (a) of the EMA 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.

EMA informed the Ombudsman on 7 April 2009 that the communication from the EC to the 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, EMA 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 EMA reviews an application for marketing approval of a new generic version of an already approved medicine. Therefore, EMA's 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, EMA commented on the volume of the requested documents. EMA stated that the documents comprised 300,000 – 400,000 pages, and that it would be a long and complex work to redact the documents.

We did not agree. We only asked 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 were only interested in placebo-controlled trials. The Danish Drug Agency had granted us access to these reports for a third anti-obesity drug, sibutramine, and, contrary to EMA, the agency did not see the amount of pages as a problem (we had been told that there were about 20,000 pages in total, or vastly less than what EMA estimated for a drug, and many of these 20,000 pages would be irrelevant for us, as we were interested in the bulk of the reports).

Finally, the clinical study reports are finely structured, which can be seen in the guidance EMA distributes to the companies, and it therefore couldn't be "a long and complex work to redact the documents", as EMA claimed. It should be a very quick and easy task.

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

1) EMA had 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, we felt EMA violated The Declaration of Helsinki, which is about universal human rights, and, furthermore, EMA 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 Declaration of Helsinki 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.

Our letter to the Ombudsman 31 Aug 2009

In the summer of 2009, Bernhard Hofstötter from the Ombudsman Institution phoned us about practical issues related to the volume of the data we had requested. We followed up on our telephone conversation by sending a letter to the Ombudsman and Hofstötter on 31 August 2009

informing them that we had received unpublished material from the Danish Medicines Agency a week earlier on the anti-obesity drug, sibutramine.

Germany was the first country in the EU to approve this drug, in 1999, but sibutramine was suspected to increase the risk of abuse and cardiovascular disease, and only after the Committee for Proprietary Medical Products had reviewed the drug was it approved in Denmark in 2001.

We applied for access to the clinical study reports of the placebo-controlled clinical trials and corresponding trial protocols of sibutramine in June 2007 and were granted access from the Danish Drug Agency in June 2008. The company, Abbott, complained to the Ministry of Health, but on 3 July 2009, the minister upheld the Agency's decision.

We received 36 binders (14,309 pages) that included 56 clinical study reports. As we had not received the appendices (which also included the protocols), we repeated our request that we also needed the protocols. From our experience, a protocol consists of less than 100 pages.

Of the 56 study reports, 27 primarily investigated weight reduction or maintenance, 9 cardiovascular risks, 3 risk of abuse and 4 tolerability and safety. The remaining 13 were less important to our project; e.g. 4 were on depression (sibutramine was originally developed for treating depression) and 7 measured less relevant outcomes.

We confirmed that the clinical study reports are finely structured, as stated in our previous letters, and that it therefore cannot be ”a long and complex work to redact the documents,” as EMA had claimed. It should be a quick and easy task. To demonstrate this, we mailed an example of a clinical study report on a pivotal trial (SB1047) to the Ombudsman by special delivery.

The clinical study reports and tables that describe the two pivotal trials BPI852 and SB1047 consist of 1430 and 283 pages, respectively. BPI852 is by far the largest study report, as the average size of a study report with tables is only 256 pages. We expected the clinical study reports on orlistat and rimonabant to be of similar sizes.

We had been asked to specify in more detail the material we were applying for, and we noted that we would like to have access to the clinical study reports, including appendices and protocols, of the phase III studies as specified in the Scientific Discussion of the EPARs on orlistat (47) and rimonabant (48).

This comprised 7 studies on orlistat and 8 on rimonabant (47,48). Thus, we were only interested in 15 studies. For comparison, we obtained reports on 56 studies on sibutramine from the Danish Drug Agency. In the copies we received from the Danish Drug Agency, patient numbers and descriptions of individual adverse events were redacted. We believed this precaution was completely unnecessary, as we had no way of knowing which concrete patients had been described. A whole page with adverse events that should have been redacted (p67 in SB1047) was overlooked, but it did not provide any clues that might lead to identification of individual patients.

Inspection of EMA’s files by the Ombudsman Institution 6 October 2009

Two people from the Ombudsman Institution inspected the files relevant for our request on 6 October 2009. The inspection showed that the documentation for orlistat amounted to approximately 1,500-2,000 pages in total for each of the seven trials. For rimonabant, it amounted to an estimated 4,000-26,000 pages per study.

EMA provided the two visitors with copies of the tables of contents of the documents inspected, but pointed out that in EMA’s view, the tables of contents formed part of confidential documents and should therefore “not be disclosed to the complainants at this stage.”

Press release from the Ombudsman 7 June 2010

We received no more letters for the next eight months. On 7 June 2010, the Ombudsman published a press release in which he criticised EMA for maladministration (49). The Ombudsman stated:

"During his investigation, the Ombudsman inspected the relevant reports and protocols. He concluded that the documents did not contain information on the composition of the anti-obesity drugs, nor did they contain other commercially confidential information. In his view, their disclosure would consequently not undermine commercial interests. The Ombudsman, therefore, criticised EMA's refusal to grant access to the reports and protocols as an instance of maladministration. He called on EMA to disclose the documents or provide a convincing explanation as to why access cannot be given. EMA is invited to submit a detailed opinion by 31 August 2010."

In his recommendation (50), The Ombudsman did not take a definitive stance on whether an overriding public interest existed, as this question only needed answering if disclosure undermined commercial interests. Also, he did not take a definitive position regarding whether the presence of 'personal data' could entitle EMA to redact the documents. He noted that the requested documents do not identify patients by name but by their identification and test centre numbers, and he concluded that the only 'personal data' are those identifying the study authors and principal investigators and to redact this would be a quick and easy task.

EMA promises to disclose the documents 31 Aug 2010

Thomas Lönngren wrote to the Ombudsman on the last day of the deadline he had been given that EMA would disclose the data we had requested.

We were very puzzled by Lönngren's letter. EMA had been completely resistant to our arguments and those of the Ombudsman, although we believe they were very convincing. Lönngren now seemed to have turned around 180 degrees, and he didn't give a clue in his letter as to why he had changed his opinion so radically. In fact, if one only read this letter, one would think that EMA had favoured disclosure of the data all the time. Lönngren wrote that:

"...the Agency is currently engaged in the finalization of a new policy on access to documents (related to the authorisation and supervision of medicinal products for human and veterinary use) aimed at increasing transparency while balancing the need to protect public and private interests that are legally recognized."

"...It is necessary to ensure with concrete steps the widest possible access to documents originated, received, or held by the Agency..."

"...the Agency shares the Ombudsman's reasoning and considers that the decision to refuse access to clinical study reports and the corresponding trial protocols in this case should be revised and that the applicant should be granted access to the requested documents."

"The Agency would also like to highlight that for future requests for access to clinical trial reports, it will apply the same principles."

"The Agency notes that as the scope of the commercial interest exception cannot be excluded *a priori* but should be examined *in concreto* on a case-by-case basis also further to consultation with the authors of the received documents and that *in specific and concrete* circumstances in which the disclosure of the documents might undermine the commercial interests of natural or legal persons, it will consider the need to redact part of the documents in line with the limits and the principles of Regulation (EC) 1049/2001."

"The Agency will do its utmost to implement its decision as quickly as possible, in any case within the next 3 months at the latest. The Agency will keep the European Ombudsman promptly informed of the exact implementation date."

Concluding remarks

It would be interesting to know what motivated EMA to change its stubborn resistance against disclosure. It was very likely the Ombudsman's conclusion about maladministration EMA couldn't ignore, which appeared in his press release, and which might have led to political pressures by members of the European Parliament.

It probably helped that the Ombudsman was involved in another case at the same time as ours. Liam Grant from Dublin, Ireland, whose son had committed suicide in 1997 while he was on isotretinoin, which is a drug used to treat severe acne, asked in April 2008 EMA for reports on suspected serious adverse reactions to the drug, such as reactions giving rise to suicidal tendencies. (51,52). The request was refused by EMA, which argued that EU transparency rules did not apply to serious adverse reaction reports. EMA also emphasised that their release would not benefit EU citizens because it could result in circulation of data that might prove to be misleading or unreliable.

Liam Grant complained to the Ombudsman who suggested that, as part of a proactive information policy, EMA could provide additional context designed to render such data and their significance more readily comprehensible by the public.

The Ombudsman published a press release on 10 May 2010 (52). EMA had argued that the EU transparency rules (Regulation 1049/2001 on access to documents) did not apply to the suspected serious adverse reaction reports. The Ombudsman noted that, in his view, the EU transparency rules apply to all documents held by EMA, and he added: "EMA plays a crucial role in the approval and monitoring of medicines placed on the market. Since its work has a direct impact on the health of European citizens, it is of utmost importance for EMA to give the widest possible access to documents and also to pursue a pro-active information policy for the benefit of citizens.

The Ombudsman published a second press release on 11 August 2010 (53) where he mentioned:

"EMA accepted the Ombudsman's recommendation to give access to the documents by announcing the release of the adverse reaction reports. The Ombudsman will take account of EMA's announcement when drafting the decision closing his investigation."

We met so much resistance from EMA that we didn't think we would succeed. We are deeply grateful for the Ombudman's determination and believe the successful outcome of our complaint to the Ombudsman is related to his personality. The legal issues are not entirely clear and there is room for interpretation. A weaker Ombudsman might therefore not necessarily have brought our case and the acne case to a successful completion.

Our case sets an important precedent that makes it much easier for others to get access to clinical study reports and protocols. This is very important progress for the health of our citizens. There is something fundamentally wrong with our priorities in health care if commercial success is dependent on withholding data that are important for rational decision-making for doctors and patients. It seems we are on the right course. The FDA, for example, has formed an internal Transparency Task Force to develop recommendations for making useful information about FDA activities and decision making more readily available to the public (51). And on 30 November 2010, EMA declared it would widen public access to documents (54).

We recommend FDA and other drug agencies to follow suit. The access should be quick (e.g. 3 months) and in a useful format. Drug agencies should get rid of the huge paper loads and require

electronic submissions from the drug companies, including the raw data, which should also be made publicly available.

EMA's last letter was unclear: "The Agency will do it utmost to implement its decision as quickly as possible, in any case within the next 3 months at the latest. The Agency will keep the European Ombudsman promptly informed of the exact implementation date."

It was not clear whether the 3 months is the deadline for sending the reports to us, for implementing its new policy, or both. We received the data we requested from EMA 1 February 2011, which in some cases included individual patient data.

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