Opening up data at the European Medicines Agency

Widespread selective reporting of research results means we don't know the true benefits and harms of prescribed drugs. **Peter Gøtzsche** and **Anders Jørgensen** describe their efforts to get access to unpublished trial reports from the European Medicines Agency

Doctors cannot choose the best treatments for their patients despite the existence of hundreds of thousands of randomised trials. The main reason is that research results are being reported selectively. Comparisons of published drug trials with unpublished data available at drug regulatory agencies have shown that the benefits of drugs have been much over-rated[1-3] and the harms under-rated.[4] Comparisons of trial protocols with published papers have also shown widespread selective reporting of favourable results.[5 6]

Selective reporting can have disastrous consequences. Rofecoxib (Vioxx) has probably caused about 100 000 unnecessary heart attacks in the United States alone,[7] and class 1 antiarrhythmic drugs probably caused the premature death of about 50 000 Americans each year in the 1980s.[8] An early trial found nine deaths among patients taking the antiarrhythmic drug and only one among those taking placebo, but it was never published because the company abandoned the drug for commercial reasons.[9]

Allowing researchers access to unpublished trial reports submitted to drug regulatory agencies is important for public health. Such reports are very detailed and provide more reliable data than published papers,[1-4] but it has been virtually impossible to get access to them. We eventually succeeded in getting access to reports held by the European Medicines Agency (EMA) after three years of trying. Our case has set an important precedent, and we summarise here the process and the arguments.

Our application for access

On 29 June 2007 we applied for access to the clinical study reports and corresponding protocols for 15 placebo controlled trials of two anti-obesity drugs, rimonabant and orlistat. The manufacturers had submitted the reports to the EMA to obtain marketing approval in the European Union. We explained that we wanted to explore the robustness of the results by adjusting for the many missing data on weight loss and to study selective publication by comparing protocols and unpublished results with those in published reports.

The information was important for patients because anti-obesity pills are controversial. The effect on weight loss in the published trials is small,[10] and the harms are substantial. People have died from cardiac and pulmonary complications[11] or have experienced psychiatric disturbances, including suicidal events,[12] and most of the drugs have been deregistered for safety reasons.

A basic principle in the European Union is to allow its citizens the widest possible access to the documents its agencies possess (box 1).[13] But there are exemptions, and the EMA refuses access if disclosure would threaten commercial interests unless there is an over-riding public interest.[14] We argued in our first letter to the EMA that secrecy was not in the best interests of the patients because biased reporting of drug trials is common.[2 5] Furthermore, we hadn't found any information that could compromise commercial interests in 44 trial protocols of industry initiated trials we had reviewed previously.[5]

Without any comment on our arguments, the EMA replied that the documents could not be released because it would undermine commercial interests. We appealed to the EMA's executive director, Thomas Lönngren, and asked him to explain why the EMA considered that the commercial interests of the drug industry should over-ride the welfare of patients. We argued that the EMA's attitude increased the risk of patients dying because their doctors prescribed drugs for them without knowing what the true benefits and harms were. He sent us a similar letter to the EMA's first letter, ignoring our request for clarification, and told us we could lodge a complaint with the European ombudsman, which we did.

Over the following three years the EMA put forward several arguments to avoid disclosing the documents: protection of commercial interests, no over-riding public interest, the administrative burden involved, or the worthlessness of the data to us after the EMA had redacted them (box 2). It also did not respond to the ombudsman's letters before his rather generous deadlines had run out.

Protection of commercial interests

Protection of commercial interests was the EMA's over-riding argument. It would undermine the protection of commercial interests to allow us access, it said, as the documents represented the full details of the clinical development programme and the most substantial part of the applicant's investment. Competitors could use them as a basis for developing the same or a similar drug and gather valuable information on the long term clinical development strategy of the company to their own economic advantage.

We explained that the clinical study reports and protocols are based on well known principles that can be applied to any drug trial; that the clinical study reports describe the clinical effects of drugs; and that nothing in the EMA's guidelines for preparation of such reports indicates that any information included in them can be considered a trade secret. The trial protocols are always sent to the clinical investigators, and it is unlikely that companies would have left in any information that could be of commercial value (such as a description of the drug synthesis). We also noted that the clinical study reports and trial protocols represent the last phase of drug development, which has been preceded by many years of preclinical development. Other companies could hardly use them as a basis for developing similar drugs. In fact, unpublished trial data are generally less positive than published ones,[1-6] and competitors would therefore be less

likely to start drug development if they had access to the unpublished results. Other companies are more likely to be interested in in vitro, animal, and early human studies, and drug companies have no problems with publishing such studies because the results may attract investors.

The European ombudsman, P Nikiforos Diamandouros, considered that commercial interests might be at stake but noted that the risk of an interest being undermined must be reasonably foreseeable and not purely hypothetical. He could not see that access would "specifically and actually" undermine commercial interests. He inspected the relevant reports and protocols at the EMA and concluded that the documents did not contain commercially confidential information. He therefore criticised the EMA's refusal to grant us access.

Over-riding public interest in disclosure

Even if commercial interests were undermined by disclosure, access would still have to be granted if there was an over-riding public interest. The EMA argued that it could not identify any over-riding public interest and remarked that the evaluation of safety and efficacy of drugs is its responsibility—the EMA constantly monitors drugs and updates its assessment reports and requires changes in product information as appropriate.

We considered this insufficient. Monitoring adverse effects reported by doctors to drug agencies would not have revealed that rofecoxib causes heart attacks. Few such events are reported, and heart attacks are common in people with arthritis. Postmarketing passive surveillance systems can therefore usually not detect whether a drug leads to more heart attacks than expected; randomised trials are needed for this.

We provided more evidence of the detrimental effects of selective publication but to no avail. The EMA continued to claim that we had not documented the existence of an over-riding public interest. We noted that we could not prove this in this specific case because we were denied access to the data, but we drew attention to the fact that the total number of patients in the main clinical studies of orlistat differed according to the source of the information: published reports, the EMA's website, and the website of the US Food and Drug Administration.

The ombudsman indicated that we had established an over-riding public interest, but he did not take a definitive stance on whether an over-riding public interest existed because this question needed answering only if disclosure undermined commercial interests. He asked the EMA to justify its position that there wasn't an over-riding public interest, but the EMA avoided replying by saying that we had not given evidence of the existence of such an interest. We believe that we had. Furthermore, the EMA's argument was irrelevant.

Box 1 | **Basic principles on citizens' access to EU documents**[13]

"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."

"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."

Box 2 | **The path to the data**

The delays on our part amounted to 130 days (11% of the time); we awaited replies for 1028 days.

29 Jun 2007: We asked the EMA to provide access to the clinical study reports and their corresponding protocols on rimonabant and sibutramine

20 Aug 2007: The EMA replied that the documents could not be released because they came under the exception of commercial interests

24 Aug 2007t We explained that the EMA's lack of transparency violated basic principles in the EU treaty and that it leads to suboptimal treatment of patients

17 Sept 2007: With no comment on our arguments, the EMA referred again to commercial interests and noted we could institute court proceedings against the EMA or complain to the European ombudsman

8 Oct 2007: We appealed to the ombudsman, noting that the published literature on drugs is flawed and arguing that protocols and study reports did not disclose anything that could undermine commercial interests

30 Jan 2008: The EMA replied to two letters from the ombudsman, referred to protection of commercial interests and mentioned that it could not identify any over-riding public interest that could justify disclosure of the requested documents

26 Feb 2008: We told the ombudsman that the EMA had failed to explain why commercial interests would be undermined

28 Apr 2008: The EMA replied to the ombudsman that it needed to protect the data against unfair commercial use; that evaluating the balance between benefits and risks of medicines is the EMA's job; and that redaction of personal data would cause disproportionate effort

17 Jun 2008: In our reply to the ombudsman, we argued against this and noted that if commercial success depends on withholding data that are important for rational decision making by doctors and patients, there is something fundamentally wrong with our priorities in healthcare

22 Jan 2009: The ombudsman proposes a friendly solution to the EMA and asks it to grant us access to the documents or provide a convincing explanation why such access cannot be granted

26 Feb 2009: The EMA restates the commercial interests; claims that we have not given evidence of an over-riding public interest; and refers to the workload involved in redacting the documents

10 Mar 2009: The ombudsman again proposes a friendly solution to the EMA and asks it to clarify its reasoning

7 Apr 2009: The EMA repeats its previous arguments.

19 May 2009: We again counter the EMA's arguments: the EMA has provided no evidence that the documents are commercially sensitive; many patients had been harmed by selective publication of trial data on COX 2 inhibitors; and redacting the documents should be quick and easy

31 Aug 2009: We tell the ombudsman that we have received trial data from the Danish Medical Agency on a third anti-obesity drug, sibutramine

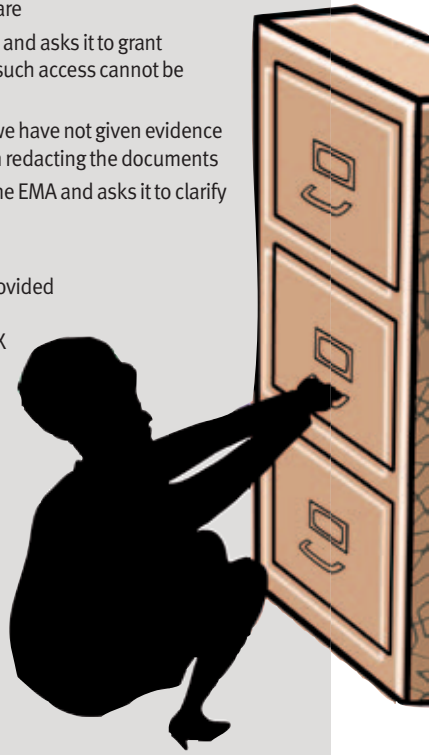
6 Oct 2009: The ombudsman goes to the EMA to inspect the documents we had requested

19 May 2010: The ombudsman issues a draft recommendation that the EMA should grant us access to the documents or provide a convincing explanation as to why not

7 Jun 2010: In a press release the ombudsman accuses the EMA of maladministration because of its refusal to grant access

31 Aug 2010: The EMA informs the ombudsman that it will provide access

1 Feb 2011: We receive the data



A suspect asked for his alibi on the day of the crime doesn't get off the hook by asking for someone else's alibi.

Administrative burden

According to the EMA, the redaction of (unspecified) "personal data" would cause the EMA a disproportionate effort that would divert attention from its core business, as it would mean redacting 300 000-400 000 pages. This was surprising. The Danish Drug Agency had not seen the workload as a problem when it granted us access to the reports for the anti-obesity drug sibutramine, which was locally approved in Denmark. The 56 study reports we received comprised 14 309 pages in total, and we requested only 15 study reports from the EMA (the pivotal studies described in the European Public Assessment Reports (EPARs) on rimonabant and orlistat). The ombudsman declared that the EMA had overestimated the administrative burden involved.

Worthlessness of data after redaction

The EMA argued 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."

From what we know of clinical trial reports and protocols it struck us as odd that they would contain so much personal data that the documents became worthless. The ombudsman 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 information would be quick and easy.

The EMA also remarked that a possible future release of the assessment reports of the EMA's Committee for Medicinal Products for Human Use and the (co)rapporteur assessment reports "could satisfy the request of the complainants." These reports were not available and they would have been worthless to us because they are merely summaries used for regulatory decisions.

Maladministration

The EMA was completely resistant to our arguments and those from the ombudsman. However, after the ombudsman accused the EMA of maladministration in a press release on 7 June 2010,[15] three years after our request, the EMA reversed its stance. The EMA now gave the impression that it had favoured disclosure all the time, agreed with the ombudsman's reasoning, and noted that the same principles would be applied for future requests for access but that it would consider the need to redact part of the documents.

The EMA's last letter was unclear: "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."

It was not clear whether the three months was the deadline for sending the reports to us, for implementing its new policy, or both. We received the data we requested from the EMA on 1 February 2011, which in some cases included individual patient data in anonymised format, identified by individual and test centre numbers.

Concluding remarks

According to the EMA's responses to the ombudsman, the EMA put protecting the profits of the drug companies ahead of protecting the lives and welfare of patients. Moreover the EMA's position is inconsistent because it resisted requests to give access to trial data on adult patients while providing access to data on paediatric trials, in accordance with EU legislation.[16] The Declaration of Helsinki gives authors the duty to make publicly available the results of their research on humans.[17] The declaration also says that, "Medical research involving human subjects must . . . be based on a thorough knowledge of the scientific literature." If the knowledge base is incomplete, patients may suffer and cannot give fully informed consent[9] and research resources are wasted. The EMA should be promoting access to full information that will aid rational decision making, not impede it.

Our case sets an important precedent. On 30 November 2010 the EMA declared it would widen public access to documents, including trial reports and protocols.[18] We recommend that the FDA and other drug regulatory agencies should follow suit. Access should be prompt—for example, within three months of the regulator's decision—and documents should be provided in a useful format. Drug agencies should get rid of the huge paper mountains and require electronic submissions from the drug companies, including the raw data, which should also be made publicly available.

Peter C Gøtzsche professor
Anders W Jørgensen PhD student, Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Dept 3343, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
Correspondence to: P C Gøtzsche, pcg@cochrane.dk
Accepted: 7 March 2011
Contributors and sources: PCG wrote the first draft, both authors commented on it and are guarantors.
Funding: Sygekassernes Helsefond and Rigshospitalet, University of Copenhagen.
Competing interests: None declared.
All documents in this case (133 pages) are available at www.cochrane.dk/research/EMA, together with a comprehensive 26 page report of the case including 54 references.
Provenance and peer review: Not commissioned; externally peer reviewed.

1 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252-60.
2 Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine—selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003;326:1171-3.
3 Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: a review of publication and presentation. *PLoS Med* 2008;5:e217.
4 Healy D. Let them eat Prozac. New York University Press, 2004.
5 Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291:2457-65.
6 Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009;361:1963-71.
7 Lenzer J. FDA is incapable of protecting US "against another Vioxx." *BMJ* 2004;329:1253.
8 Moore TJ. Deadly medicine: why tens of thousands of heart patients died in America's worst drug disaster. Simon & Schuster, 1995.
9 Cowley AJ, Skene A, Stainer K, Hampton JR. The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. *Int J Cardiol* 1993;40:161-6.
10 Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for obesity and overweight. *Cochrane Database Syst Rev* 2003;4:CD004094 (updated 2009).
11 Mundy A. Dispensing with the truth. St Martin's Press, 2001.
12 Food and Drug Administration. FDA briefing document. NDA 21-888. Zimulti (rimonabant) tablets, 20 mg. 2007. www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf.
13 Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. *Official Journal of the European Communities* 2001;L145:43-8. www.europarl.europa.eu/RegData/PDF/r1049_en.pdf.
14 Rules for the implementation of Regulation (EC) No 1049/2001on access to EMEA documents. EMEA/MB/203359/2006 Rev 1 Adopted. Management board meeting 19 December 2006. www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500070829.pdf.
15 Diamandouros PN. Ombudsman: European Medicines Agency should disclose clinical reports on anti-obesity drugs. European ombudsman press release, 7 June 2010. www.ombudsman.europa.eu/press/release.faces/en/4940/html.bookmark.
16 Choonara I. Regulation of drugs for children in Europe. *BMJ* 2007;335:1221-2.
17 World Medical Association. Declaration of Helsinki—ethical principles for medical research involving human subjects. 2008. www.wma.net/en/30publications/10policies/b3/index.html.
18 EMA. European Medicines Agency widens public access to documents. Press release, 30 November 2010. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/11/news_detail_001158.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp.

Cite this as: *BMJ* 2011;342:d2686

Response on bmj.com

"The authors make what appears to be a compelling call for more transparency by the regulatory authorities. However, they do so by ignoring the steps taken by the European Medicines Agency since it was established in 1995 and the latest actions and policy adopted over the last few years." Andreas Pott, acting executive director, EMA

To submit a rapid response, go to any article on bmj.com and select "Respond to this article"

EMA must improve the quality of its clinical trial reports

Corrado Barbui, **Cinzia Baschirotto**, and **Andrea Cipriani** find that the results of phase III studies are poorly and inconsistently documented in the EMA's drug assessment reports. Better reporting would make them more useful for doctors, researchers, and consumers

In Europe, new drugs are approved or rejected on the basis of the results of studies carried out by the manufacturer and submitted to the European Medicines Agency. However, the transparency of the approval process has been criticised.[1 2] Calls have been made for the European Public Assessment Report (EPAR), a summary of the grounds for granting marketing authorisation (box 1), to include additional information on critical points examined and discussed during assessment such as whether a drug is approved by majority vote, the reasons for the minority's opposition, and decisions of other licensing bodies, in a timely and user friendly format.[1 2]

Surprisingly, no criticism has been raised about the quality of the information that is currently available, especially the quality of reporting of phase III studies. This is an important aspect considering that new drugs are approved on the basis of the results of studies carried out by the manufacturer. Accessing the results of these studies may be relevant for doctors, who need to know the size of effect of newly licensed drugs for prescribing reasons, and for researchers involved in systematic reviews, who may need to use EPARs to access unpublished data for meta-analyses because not all the study reports that are submitted to regulatory agencies are published in the international literature.[5] Consumers and the wider public may also want to check the basis for approval of new drugs.[6] We use the example of drugs for psychiatric disorders to highlight deficiencies in current reporting.

Box 1 | Assessment of new drugs in Europe

European Medicines Agency (www.emea.europa.eu)

The European Medicines Agency (EMA) is an agency of the European Union responsible for the scientific evaluation of medicines developed by drug companies for use in EU countries. The EMA's decisions on new or old medicines relating to changes in therapeutic indications, approval, suspension, or withdrawal of a product have to be accepted by all EU members.[3]

European public assessment report

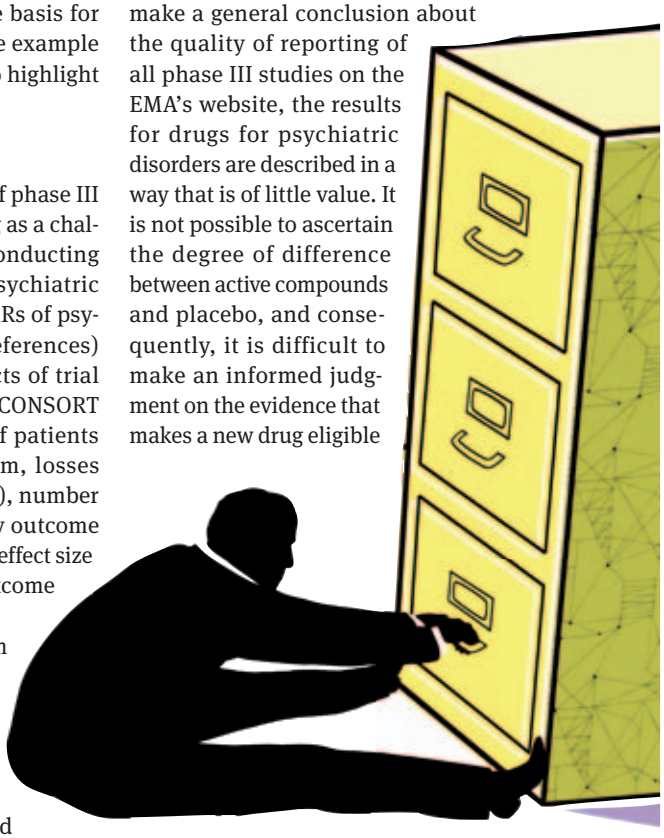
Once the EMA has given marketing authorisation for a drug, it publishes a scientific assessment called the European Public Assessment Report (EPAR). The EPAR, written in agreement with the industry,[4] summarises the documentation produced by the manufacturer and describes procedures that led to the EMA approval. EPARs are published on the EMA's website after commercially confidential information has been deleted (www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp).

EMA reporting standards

The quality of reporting of results of phase III studies in EPARs has been emerging as a challenging problem for researchers conducting systematic reviews of drugs for psychiatric disorders.[7 8] We examined the EPARs of psychiatric drugs (see bmj.com for references) for information on four key aspects of trial reporting highlighted in the 2010 CONSORT statement[9]—that is, the number of patients randomised to each treatment arm, losses during follow-up (plus the reasons), number of patients included in the primary outcome analysis, and absolute numbers and effect size (with precision) for the primary outcome analysis (box 2).

The EMA approved eight drugs from 2004 to 2009 for 15 psychiatric indications (table 1). Of the 70 phase III randomised trials described in the EPARs, 34 (49%) reported the number of patients allocated to each treatment arm, 19 (27%) reported drop-outs with reasons, 30 (43%) the number of patients analysed for primary outcome, and nine (13%) efficacy in terms of absolute numbers. Only six of these nine trials gave an effect size with its precision. This lack of data and erratic reporting made it impossible to use meta-analysis to calculate a summary measure of the overall treatment effect for any of the newly licensed drugs. Table 1 shows that the quality of reporting is improving for some items (numbers of patients in each treatment arm and included in the efficacy analysis) but not for others (drop-outs, efficacy results).

Although this example cannot be used to make a general conclusion about the quality of reporting of all phase III studies on the EMA's website, the results for drugs for psychiatric disorders are described in a way that is of little value. It is not possible to ascertain the degree of difference between active compounds and placebo, and consequently, it is difficult to make an informed judgment on the evidence that makes a new drug eligible



for approval. Percentages are often reported without absolute numbers and without denominators, mean change scores are almost always reported without a measure of precision, and descriptive presentations of study findings may omit key figures, such as the number of patients randomised to each treatment arm. For example, in the EPAR for melatonin, one phase III clinical trial is described as follows: "523 patients entered the study, 453 were randomised and 334 were included in the Full Analysis Set, 169 in the Circadin group and 165 in the placebo group."[10] The number of patients randomised to each treatment arm cannot be determined from the description. This is not a minor point; without this information it is not possible to calculate any summary measure of treatment effect, and the potential exclusion of randomised patients from the analysis may result in biased estimates of treatment effects.[11]

Lack of consistency is another big problem. One EPAR may contain the required details for some studies but not for others, and no background logic seems to explain this inconsistently organised reporting.

Better reporting is possible

The provision of information on the websites of regulatory authorities in different countries has been shown to vary widely. A 2008 survey of six national regulatory agencies (United States, Canada, UK, France, Australia, and New Zealand) and the EMA showed that only the US Food and Drug Administration, the Canadian and French agencies, and the EMA provided public assessment reports for each new drug approved.[12] The FDA information included comprehensive reports of clinical trials, whereas other agencies provided only abbreviated and summarised information. The FDA documents, however, have more recently been described as lengthy, inconsistently organised, and weakly summarised, making the information they contain practically inaccessible.[13] In June 2009 the commissioner of the FDA announced a major transparency initiative with the goal of better explaining the FDA's actions by providing information that supports clinical medicine, biomedical innovation, and public health.[14] This initiative has already led to several draft proposals, although the FDA has not yet implemented new guidance on reporting trials in FDA reviews.

We argue that the EMA should develop and implement a similar transparency initiative. As initial step, a more informative description of the results of phase III studies would require no additional costs and would not require the release of any proprietary information. We suggest that the EPARs should include, for each phase III study, a tabular description of basic information on patient disposition and outcomes, together with the trial identification number that uniquely identifies a specific study (such as that from clinicaltrial.gov or similar). Table 2 shows an example template

Box 2 | Search strategy and methods used to extract information from EPARs on psychiatric drugs

Search strategy

We did a systematic manual search of documents published on the EMA's website (January 2010). We identified the European Public Assessment Reports (EPARs) of approved drugs for schizophrenia, acute mania and prevention of relapse, agitation in schizophrenia and bipolar disorder, major depressive disorder, generalised anxiety disorder and insomnia.

Data extraction and presentation

Working independently and in duplicate, two reviewers read the EPARs and identified the studies described as phase III clinical trials. For each of these, data were extracted on the following basic aspects of trial reporting: number of patients randomised per treatment arm, losses during follow-up, and number of patients included in the primary outcome analysis. Availability of the results of the primary outcome analysis was also investigated in terms of (*a*) absolute numbers for each treatment arm: number of subjects with the outcome of interest/total number of subjects (dichotomous outcomes); total number of subjects, mean end point or change score at the outcome of interest, standard deviation or standard error (continuous outcomes) and (*b*) effect size with its precision. We used a tabular approach to data presentation.

Table 1 | Availability of information required in the CONSORT 2010 statement from European Public Assessment Reports for phase III studies of drugs approved for psychiatric disorders

				No of studies reporting:					
Year of report	Drug	Indication	No of phase III studies	No randomised to each treatment arm	Losses after randomisation with reasons	No analysed for primary outcome	Efficacy results (absolute numbers)	Effect size and its precision	Meta-analysis possible
2004	Olanzapine	Schizophrenia	5	0	0	0	0	0	No
2004	Olanzapine	Acute mania and prevention	6	1	0	0	0	0	No
2004	Olanzapine	Agitation	3	0	0	0	0	0	No
2005	Aripiprazole	Schizophrenia adults	5	1	0	0	1	1	No
2005	Duloxetine	Major depressive disorder	7	0	0	0	0	0	No
2005	Zaleplon	Insomnia	4	0	0	0	0	0	No
2006	Pregabalin	Generalised anxiety disorder	7	1	1	1	1	1	No
2007	Aripiprazole	Agitation	3	3	0	3	0	0	No
2007	Melatonin	Insomnia	2	1	0	2	1	1	No
2007	Paliperidone	Schizophrenia	5	5	5	4	0	0	No
2008	Agomelatine	Major depressive disorder	7	7	6	7	5	2	No
2008	Aripiprazole	Acute mania and prevention	8	7	5	6	1	1	No
2008	Duloxetine	Generalised anxiety disorder	5	5	0	4	0	0	No
2008	Olanzapine depot	Schizophrenia	2	2	2	2	0	0	No
2009	Aripiprazole	Schizophrenia adolescents	1	1	0	1	0	0	No
Total			70	34	19	30	9	6	—

Table 2 | Template for better reporting of patient disposition and results of the primary outcome analysis in EPARs

Clinical trial identification code:_____	Investigational drug	Control drug/ placebo
No of participants		
Randomised	.....	.....
Received intended treatment	.....	.....
Completed	.....	.....
Withdrawn (with reason: lack of efficacy, adverse events, other reasons)	.....	.....
Continuous primary efficacy results		
No of participants included	.....	.....
Mean (SD) baseline score of primary outcome measure	.....	.....
Mean (SD) end point score of primary outcome measure	.....	.....
Effect size (confidence interval)	.....	.....
Dichotomous primary efficacy results		
No of participants included	.....	.....
No of participants meeting primary outcome criteria	.....	.....
Effect size (confidence interval)	.....	.....

with a minimum set of information to properly describe the results of phase III studies of drugs for psychiatric disorders. The template could be adapted for other clinical areas and circumstances. Such data abstractions would be a balanced compromise between the ideal situation of having access to all original trial data and the current situation of having access to sparse and incomplete information.

Some drug companies have already started using templates to disseminate trial results. GlaxoSmithKline (GSK), for example, was required in 2004 to provide access to all published and unpublished data from GSK sponsored clinical trials in an easy and user friendly format (www.gsk-clinicalstudyregister.com), and these data have already contributed to systematic reviews and meta-analyses,[15 16] with an obvious added value for the scientific community.

Although a tabular description of basic information for each phase III study would mainly be designed to meet the needs of researchers doing systematic reviews and meta-analyses, the EMA might also attempt to target broader audiences of doctors and consumers. Doctors may benefit from summaries of randomised evidence presented in the EPARs, and these summaries could be developed following the example of the "summary of findings" table in Cochrane reviews. These tables provide key information concerning the quality of evidence, the magnitude of effect of the intervention examined, and the sum of available data on all important outcomes. A randomised trial showed that summary tables improve understanding and rapid retrieval of key findings when compared with reports with no table.[17] Similarly, consumers may be interested in a concise and straightforward summary of the benefits and side effects of the new drug, and this summary could follow a structure similar to that of the drug facts box, a one page table quantifying outcomes with and without the new drug developed in the US. Providing consumers with a drug facts box has been shown to improve their knowledge of the benefits and side effects of prescription drugs.[18]

Better provision of information on the EMA's website would improve its value with relatively little effort

It should be highlighted, however, that these or similar reporting templates for doctors and consumers can be produced only if the results of phase III study are fully available. Thus our suggested tabular description of basic information on patient disposition and outcomes would represent a minimum but essential prerequisite for any further development of data presentation. This further development could be done by independent organisations or by the EMA.

Better provision of information on the EMA's website would improve its value with relatively little effort. Doctors would have the opportunity to know the magnitude of effect of newly licensed drugs, authors of systematic reviews and meta-analyses would access trial results that might never be published in scientific journals, and consumers would have the chance to closely monitor the whole drug approval process aiming for continuous improvement.

Corrado Barbui associate professor of psychiatry
Cinzia Baschirotto researcher
Andrea Cipriani lecturer in psychiatry, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

Correspondence to: C Barbui, Section of Psychiatry and Clinical Psychology, Policlinico G B Rossi, Piazzale L A Scuro 10, 37134 Verona, Italy corrado.barbui@univr.it

Accepted: 15 March 2011

Contributors and sources: C Barbui and A Cipriani have long experience in issues related to the methodology of systematic reviews and meta-analyses. C Baschirotto's MD dissertation focused on European regulations for granting marketing authorisations. C Barbui and C Baschirotto read the EMA's documentation and analysed the studies. C Barbui conceived the paper and wrote the first draft. All authors contributed to the writing, revised the text critically, and approved the final version. C Barbui is the guarantor.

Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

1 Garattini S, Bertele' V. Europe's opportunity to open up drug regulation. *BMJ* 2010;340:c1578.
2 European Medicines Agency—more transparency needed. *Lancet* 2010;375:1753.
3 Garattini S, Bertele V. Adjusting Europe's drug regulation to public health needs. *Lancet* 2001;358:64-7.
4 Garattini S. EMEA: for patients or for industry? *Pharmacoeconomics* 2005;23:207-8.
5 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252-60.
6 Garattini S, Bertele' V, Li Bassi L. Light and shade in proposed revision of EU drug-regulatory legislation. *Lancet* 2003;361:635-6.
7 Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746-58.
8 Barbui C, Cipriani A, Lintas C, Bertele V, Garattini S. CNS drugs approved by the centralised European procedure: true innovation or dangerous stagnation? *Psychopharmacol (Berl)* 2007;190:265-8.
9 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
10 European Medicines Agency. Assessment report for Circadin. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000695/WC500026808.pdf.
11 Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Burgi E, Scherer M, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009;339:b3244.
12 Vitry A, Lexchin J, Sasich L, Dupin-Spriet T, Reed T, Bertele V, et al. Provision of information on regulatory authorities' websites. *Intern Med J* 2008;38:559-67.
13 Schwartz LM, Woloshin S. Lost in transmission—FDA drug information that never reaches clinicians. *N Engl J Med* 2009;361:1717-20.
14 Asamoah AK, Sharfstein JM. Transparency at the Food and Drug Administration. *N Engl J Med* 2010;362:2341-3.
15 Aursnes I, Tvete IF, Gaasemyr J, Natvig B. Suicide attempts in clinical trials with paroxetine randomised against placebo. *BMC Med* 2005;3:14.
16 Barbui C, Furukawa TA, Cipriani A. Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *CMAJ* 2008;178:296-305.
17 Rosenbaum SE, Glenton C, Oxman AD. Summary-of-findings tables in Cochrane reviews improved understanding and rapid retrieval of key information. *J Clin Epidemiol* 2010;63:620-6.
18 Schwartz LM, Woloshin S, Welch HG. Using a drug facts box to communicate drug benefits and harms: two randomized trials. *Ann Intern Med* 2009;150:516-27.

Cite this as: *BMJ* 2011;342:d2291