Via electronic transmission

P. Nikiforos DIAMANDOUROS — The European Ombudsman

Paris, 30 August 2010

Dear Sir,

The European Medicines Agency (EMA) is responsible for evaluating the safety, efficacy and quality of drugs before and after centralised marketing authorisations and in the cases referred to in article 31 of Directive 2001/83/EC. EMA is also responsible for evaluating safety during a referral under the article 107 of Directive 2001/83/EC.

Prescrire provides independent information, by and for healthcare professionals (more about us: http://english.prescrire.org). *Prescrire* has the editorial and research capabilities to ensure the accuracy of its reviews. *Prescrire* bases its reviews of new drugs on data collected form a variety of sources, including drug regulatory agencies which hold large amounts of drug information and key data unavailable elsewhere. As of today, *Prescrire* submitted 142 requests for documentation or information to the EMA since 2005.

Unfortunately, our experience has shown too many EMA refusals to send documents and too many deleted parts in reports ultimately sent (1,2). The following 5 complaints concern the most unacceptable EMA failures to respond.

First complaint: refusal to send a Reference Member State assessment report on *rimonabant*, a dangerous anti-obesity drug that was withdrawn for safety issues from the European market some months after our request.

On 18 September 2008, *Prescrire* requested EMA for information on *rimonabant*. We requested documents following CHMP's consideration of a risk management plan for this drug in 2006. Together with EMA we managed to identify the available documents. The most relevant document was the assessment report established by the Reference Member State: the Swedish drug Agency.

On 16 October 2008, EMA refused to provide us with the Swedish report citing that this document came under the list of exceptions set out in the implementation rules of Regulation (EC) 1049/2001. Providing this information on this dangerous drug to *Prescrire* readers "*would undermine the protection of commercial interests*".

After a second request to Sir Lönngren explaining that we disagreed with this refusal, EMA provided us with documents, including the Swedish report but only 3 of the 68 pages of this report were legible: 65 pages of the 68-page report were systematically blacked out, line by line, including the date of the report (3,4).

→ We would therefore appreciate if you could ask EMA to provide us with a fully legible version of the Swedish report, and if needed with clear justification for each deleted parts all along the report.

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(Statuts sur demande)

Second complaint: refusal to provide us with any Periodic Safety Updated Reports (PSURs).

Our request on *rimonabant* included 3 PSURs cited in two safety variations related to the risk management plan. Following our requests, EMA refused to provide us with these PSURs citing "*protection of commercial interests"* (3).

In December 2008, *Prescrire* requested a PSUR related to a safety variation on *telithromycin*, a macrolide licensed in several infection diseases. On 14 January 2009, EMA refused to provide this PSUR citing "*the protection of the commercial interest*" (5).

In January 2009, *Prescrire* requested a PSUR related to a safety variation on *memantine*, a drug licensed for patients with Alzheimer disease. On 12 February 2009 and 6 March 2009, EMA refused to send us this document citing "*the protection of commercial interest*" (6).

On 9 June 2009, *Prescrire* requested a PSUR about *ivabradine*, a drug licensed for the treatment of angina pectoris. On 30 June 2009, EMA based its refusal on "*the protection of commercial interest"* (7).

Full access to information on dangerous drugs is essential for all parties involved in health care, including patients. In agreement with article 255 of the Treaty establishing the European Community, citizens have a right to access European Institution documents in application of transparency principles. There is no reason to make PSUR an exception to Regulation (EC) 1049/2001: data on adverse effects suffered by patients are public data, whether they are held by pharmaceutical companies or drug agencies. Regulation (EC) 1049/2001 states that public access "*shall apply to all documents held by an institution, that is to say, documents drawn up or received by it and in its possession, in all areas of activity of the European Union"* (article 2 point 3). And EMA rules states in "Principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents" that clinical data are not considered as confidential documents. Documents established by drug agencies could not be considered as protected by an intellectual property.

In their "Recommendations on the handling of requests for access to periodic safety update reports (PSURs)" dated November 2009, HMA and EMA discussed a way to facilitate the release of PSURs. In 2010, the French drug Agency (Afssaps) sent *Prescrire* a PSUR about the ophthalmological off-label use of *bevacizumab* (**a**).

→ We would therefore appreciate if you could ask EMA to stop systematically refusing access to PSURs and to provide us with fully legible versions of the requested PSURs, and if needed with clear justification for each deleted parts all along the report.

Third complaint: EMA refusal to provide us with mock-up packaging.

On 23 April 2009, *Prescrire* requested EMA for the colour mock-ups (primary and secondary packaging and leaflet) for *telbivudine,* a drug licensed for the treatment of chronic hepatitis B. On 5 June 2009, EMA refused to give access to these basic documents citing "*the protection of commercial interest* (…) *including intellectual property"* (8). On 9 June 2009, we sent a second request with more details to explain our request. Evidence shows that well-designed packaging help to minimise medication errors. That is why EMA makes a general check on mock-ups of medicinal products prior commercialisation. To the best of our knowledge nothing exempts mock-ups and packaging (essential parts of drug information) from being defined as "documents". Some MHRA public assessment reports already contain mock-ups of drug packaging (**b**). On 2 July, EMA again refused to give us access to these mock-ups repeating the same reasons (8).

→ We would therefore appreciate if you could ask EMA to provide us with requested mock-up packaging.

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Fourth complaint: refusal to give access to clinical data on the *dextropropoxyphene* + *paracetamol* combination.

On 16 April 2009, the referral procedure involving this combination for safety reasons had been ongoing for 400 days! *Prescrire* requested access to the Rapporteur and the Co-Rapporteur assessment reports held by the EMA. These assessment reports are "publicly accessible" according to Regulation (EC) 1049/2001 (**c**).

On 8 May 2009, EMA refused to provide us with any documents related to this referral procedure stating: "*The Agency could not identify an overriding public interest that would justify the disclosure of the concerned documents"* (9). But on 14 June 2010, the European Commission endorsed a CHMP recommendation to withdraw the marketing authorisation for products containing *dextropropoxyphene* for safety reasons. Finally, the referral procedure for this dangerous drug was ongoing during more than 800 days, and the European Decision states that marketing authorisations shall be revoked within 15 months.

You should know that, on 29 August 2010, we again requested EMA for the Rapporteur and Co-Rapporteur assessment reports.

→ We would let you know if EMA refused to satisfy this last request, so that you can help us.

Fifth complaint: EMA refusal to provide us with a Co-Rapporteur report related to topical *ketoprofen*.

Our request followed the Decision by the French Council of State (the highest administrative jurisdiction) to annul a decision taken by the French drugs agency Afssaps that led to suspend the marketing authorisations for *ketoprofen* gels because of their risk-benefit balance. The Decision of the French Council of State mentioned the assessment by the Co-Rapporteur designed by the European authorities to examine the French request under the article 107 of Directive 2001/83/EC. According to this Co-Rapporteur, the risk-benefit balance was unchanged. Therefore on 25 February 2010, *Prescrire* asked EMA to provide us with the Co-Rapporteur assessment report related to this referral.

On 17 March 2010, EMA refused to give access to this Co-Rapporteur assessment report citing the impossibility to give "*access to a document which relates to a matter where decision has not be taken"*. After a second request, EMA repeated its refusal (10).

Afssaps decision to withdraw *ketoprofen* gel was late in coming but more than welcome. There has long been evidence than *ketoprofen* gels are more harmful than beneficial in patients with mild disorders: there are less dangerous therapeutic alternatives.

→ We would therefore appreciate if you could ask EMA to provide us with the Rapporteur and Co-Rapporteur reports related to topical *ketoprofen* so that we can better understand and explain EMA's conclusions of our readers.

Conclusion. EMA's lack of transparency regarding safety data is unacceptable and leads to widespread suspicion about its regulatory decisions. In 2010, all EU citizens and health professionals are entitled to ask what kind of information is hidden behind EMA refusals and in the blacked-out parts of documentation sent to *Prescrire*. EMA was set up in order to serve patients' and citizens' interests. We therefore cannot understand why EMA drags its feet when requested to release documentation.

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Thank you for your help toward increased transparency of the EMA, which is needed to increase its accountability and citizens' trust in its decision-making.

Sincerely,

Olivier HUYGHE
For Prescrire editorial team

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a- All PSURs should be posted on EMA website without the need to request them.

b- Packaging elements are the most important source of information for patients.

c- We particularly welcome your action in favour of disclosure of "documents" before a final decision is made, whenever a public interest is at stake (Ombudsman welcomes European Parliament's suggestions to improve public access to EU documents – 11 March 2009).

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Selected references and files joined to our complaint:

1- Prescrire Editorial Staff "Legal obligations for transparency at the European Medicines Agency: Prescrire's assessment over four year" *Prescrire Int* 2009; **18** (103): 228-233.
2- Prescrire "Excessive secrecy beyond the law! Prescrire answer to Draft of "EMEA policy on the practical operation of access to EMEA documents"" 2 March 2009: 5 pages.
3- European Medicines Agency "Lettres à Prescrire" 7 October 2008 + 16 October 2008 + 30 October 2008: 4 pages au total +
4- European medicines Agency "Läkemedelsverket Acomplia Final Assessment report au FUM 027" (date blacked out): 68 pages.
5- European Medicines Agency "Lettre à Prescrire" 14 January 2008: 2 pages.
6- European Medicines Agency "Lettres à Prescrire" 12 February 2009 + 6 March 2009: 4 pages.
7- European Medicines Agency "Lettre à Prescrire" 30 June 2009: 1 page.
8- European Medicines Agency "Lettre à Prescrire" 5 June 2009 + 2 July 2009: 3 pages.
9- European Medicines Agency "Lettre à Prescrire" 8 May 2009: 2 pages.
10- European Medicines Agency "Lettres à Prescrire" 17 March 2010 +10 May 2010: 3 pages.