European Medicines Agency: transparency policy marred by too many failings

- Until late 2010, the European Medicines Agency (EMA) refused to release major documents containing clinical data, produced by pharmaceutical companies, which is not in keeping with the right of access to administrative documents that exists within the European Union. A group of Danish researchers, as well as Prescrire, which has been requesting documents from the EMA on a regular basis since the Agency was first established in 1995, filed a successful complaint against the EMA with the European Ombudsman. In 2011, the EMA committed to establishing a new transparency policy.

- Judging by its responses to Prescrire's applications for access to documents, the EMA then became more transparent, yet secrecy persisted in some areas and became more pronounced over the years. The identity of applicants such as Prescrire can now be disclosed to the pharmaceutical company that produced the document requested. The EMA has put in place a number of processes that have considerably increased response times: a queuing system; staggering the provision of documents over a period of several months; and a delay to allow drug companies to institute legal proceedings in the event of a disagreement over the disclosure of documents.

- When pharmaceutical companies have brought cases before the European courts to prevent the EMA from releasing documents relating to marketing authorisations, the EMA has refused to provide documents requested by Prescrire, citing the existence of these legal proceedings as grounds for its refusal, even when our requests were unrelated to the case.

- While the EMA struggled to meet its obligations on transparency, worrying signs emerged in the implementation of its policy of "proactive" disclosure. The EMA began spontaneously publishing large quantities of clinical data from marketing authorisation applications in 2016. But this major advance was marred by the fact that pharmaceutical companies were given the opportunity to redact (i.e. black out) large portions of these documents before their publication, including clinical data from clinical study reports.

- European citizens have the right to access clinical data related to marketing authorisation applications. This is a right that helps better protect patients.

- The EMA's failings justify an official enquiry in order to analyse their causes and enable Members of the European Parliament to take appropriate steps: ensuring that the EMA gets the additional resources it needs to fully meet its transparency obligations; strict oversight and close monitoring of any redactions made to released documents; and fair consideration of applicants with no ties to industry, such as Prescrire.

There is nothing new about drug regulatory agencies withholding information. Their reasons are known and include: a weak culture of transparency and weak transparency policy; insufficient staff; overcautiousness through fear of legal challenges by pharmaceutical companies; and lack of political or institutional oversight to ensure that agencies meet their transparency obligations (1). Yet the right of access to documents held by European institutions is a general principle in European Union (EU) law (2). Transparency is supposed to be the default position for European institutions, and non-disclosure of data the exception (3). The European Medicines Agency (EMA) is required by European regulations to apply these principles (4).

The EMA's responses to Prescrire's requests for data give an idea of its level of transparency. In our first assessment, covering the period 2005-2008, the EMA had been particularly secretive toward Prescrire, systematically refusing to disclose major documents containing clinical data produced by pharmaceutical companies (5).

Was the situation any better during the 2010s?

2010: EMA secrecy at its height

During the 2000s, Prescrire actively influenced the development of a directive that enhanced the transparency of EU drug regulatory agencies (6). Once this directive had come into effect, Prescrire regularly requested additional clinical data from the EMA in order to carry out our evaluations, especially concerning adverse effects detected after marketing authorisation had been granted, in order that we may better inform the healthcare professionals who subscribe to *Prescrire*, and thus better protect patients (5).

Refusal to release major documents on adverse effects. Companies that hold marketing authorisations are legally required to submit Periodic Safety Update Reports (PSURs) on their drugs. PSURs compile the data collected worldwide, over a given period, on a drug's adverse effects (**a**). The PSUR is submitted to the EMA, then evaluated by rapporteurs appointed among the drug regulatory agencies of EU member states (7). We asked the EMA for various PSURs between 2008 and 2010. EMA refused to disclose them during this period (8). It also refused to send us mock-ups or scans of the packaging (boxes, labelling and patient leaflets) of various drugs. These documents are useful to us so that we can evaluate the quality and safety of a drug's packaging in order to help prevent medication errors (8,9).

The appalling case of rimonabant. *Rimonabant* was authorised in the EU in 2006 to help obese or overweight patients lose weight, and it was withdrawn from the market a few years later due to its neuropsychiatric adverse effects (depression and suicidal ideation) (10). While it was on the market, we asked the EMA for the detailed report by the Swedish drug regulatory agency, including its assessment of the PSUR on *rimonabant*. As Sweden was the rapporteur country for this drug in the EU, the Swedish drug regulatory agency was the most relevant source of analyses of the evaluation data (5). The EMA sent us this report, but the equivalent of 61 of 68 pages had been redacted (blacked out) (5,8). In our email exchanges before they sent us this redacted report, the EMA implied that they would rather have sent us their own report, based on the Swedish report (9). But we wished to consult the original report.

Other refusals, sparking complaints to the European Ombudsman. The EMA also refused to send Prescrire the European report upon which France's administrative supreme court, the Conseil d'Etat, had based its decision to overturn the decision by the French drug regulatory agency (Afssaps, which later became ANSM) to suspend marketing authorisation for cutaneous *ketoprofen* due to its severe cutaneous adverse effects. The EMA also refused to share data on the *dextropropoxyphene + paracetamol* combination, which was subsequently withdrawn from the European market (8). The EMA refused both of these requests on the grounds that a European review was in progress (more on this later) (9).

In the face of all these refusals, Prescrire submitted 5 complaints about the EMA to the European Ombudsman in August 2010 citing lack of transparency and maladministration (8). The European Ombudsman is the EU body that deals with complaints about European institutions and agencies, such as the European Commission and the EMA. Complaints culminate in a "friendly solution" or in the Ombudsman issuing recommendations to the institution. The European Ombudsman can initiate an inquiry so that the Members of the European Parliament (MEPs) can take appropriate action (**b**)(11).

Late 2010: the European Ombudsman calls the EMA to order. In 2007, the EMA refused access to clinical study reports (CSRs) on two weight-loss drugs, *orlistat* and *rimonabant*, to researchers from the Nordic Cochrane Centre in Denmark, which prepares systematic reviews of scientific publications (12). Pharmaceutical companies submit clinical study reports to the EMA in support of their marketing authorisation applications. These documents contain very detailed data that can help identify methodological bias which may not be apparent in the summaries released by the EMA. At the time marketing authorisation is first granted, they are considered the most detailed documents on the drug, especially on its adverse effects (13).

The EMA's intention in refusing to disclose these reports was to protect the commercial interests of the pharmaceutical companies that produced them, and to prevent the theoretical risk that a competitor could use the data as a basis for developing a similar drug. The Danish researchers rejected this argument and complained to the European Ombudsman (12). The Ombudsman found the argument that disclosure of these clinical study reports could undermine the companies' commercial interests to be unfounded. He based his decision on: the general principle of EU law giving wide public access to documents held by European institutions, European Regulation 1049/2001 on access to administrative documents, and case law (12).

a- *A 2010 European directive brought in a requirement for pharmaceutical companies to assess their drug's harm-benefit balance in each Periodic Safety Update Report (PSUR). PSURs were renamed "periodic benefit-risk evaluation reports" (PBRERs), although the term PSUR is still widely used (ref 59).*

b- *In May 2011, a majority of Members of the European Parliament (MEPs) voted "not to grant discharge" to the EMA's 2009 budget, a procedure used to retrospectively approve (or not) the way in which EU institutions and agencies have managed their budget. The decision against the EMA was based on internal Commission audits listing major failings with regard to conflicts of interest, the quality of collected data, and access to data. The EMA was given 6 months to come up with proposals to improve its internal procedures (ref 60).*

2011 to 2017: increasing transparency, but murky areas remain

The European Ombudsman's 2010 opinion led the EMA to reconsider its view on exceptions to the right of access to documents and to reform its transparency policy (9,14). The Agency sent us the PSURs we requested. In a 2013 message issued in response to our complaints, the Ombudsman recommended that the EMA send us the packaging items we requested (15).

A policy of access to documents on request (Policy 0043). In the wake of the European Ombudsman's decision regarding the complaint by the Danish researchers, the EMA drew up its first transparency policy, which is still in effect as of early 2022. This policy, called Policy 0043, includes the rules that the EMA intends to apply to provide access to the documents in its possession. The EMA defined two types of registers. The first includes documents containing clinical data received in connection with European evaluations, such as PSURs and clinical study reports, as well as documents it produces itself, for example when it assesses a PSUR or a marketing authorisation application. These documents, containing clinical data, are deemed "*releasable*". They include the documents regularly requested by Prescrire. A second register lists documents with no clinical data, pertaining to the EMA's internal governance activities, some releasable and some non-releasable (14).

Substantial improvement overall. Beginning in 2011, we saw a great improvement overall in the EMA's responses to our requests. The Agency released almost all of the documents or other information we requested (about 40 each year).

We mainly requested information about post-authorisation decisions, on which the EMA publishes little data, and which are based on the conclusions of its marketing authorisation committee (Committee for Medicinal Products for Human Use, or CHMP) or on the evaluations of its pharmacovigilance committee (Pharmacovigilance Risk Assessment Committee, or PRAC).

To give a few examples: we requested the unpublished assessment report behind the decision to extend the use of *duloxetine* (Cymbalta°) in generalised anxiety disorder to include children, a change that was introduced through the "Posology" section of the drug's summary of product characteristics (SPC) (16). We requested the PRAC's assessment report on the PSURs on *pentoxyverine* (17). We requested a number of PSURs, e.g. one on *melatonin* (Circadin°) for an article we were preparing on the risk of angioedema (18). And we requested a PRAC assessment report on a safety signal suggesting excess mortality with *selexipag* (Uptravi°) (19).

We sometimes requested documents written before marketing authorisation had been granted, such as a clinical study report on *defibrotide* (Defitelio°), a drug authorised for use in hepatic veno-occlusive disease on the basis of very limited data (20).

The EMA also organises evaluations in order to harmonise old national marketing authorisations across Europe (21). In France, these procedures have sometimes resulted in new indications. We have regularly requested and received unpublished reports connected with these procedures. This was the case for *cefuroxime*, for example (22).

Before the launch of the public version of the European pharmacovigilance database, EudraVigilance, we used to obtain lists of reported adverse drug reactions, e.g. reports involving *thiocolchicoside*, or medication errors, e.g. errors involving vaccination techniques (7,23). We also received numerous packaging items (24).

Far fewer refusals, but worrying signs. In May 2011, the EMA refused to send Prescrire data on the risk of bladder cancer associated with *pioglitazone* (Actos°), on the grounds that providing us such data could influence the conclusions of the EMA's ongoing review of the drug's harm-benefit balance (25). The EMA's refusal was based on the exception to disclosure set out in Article 4.3 of Regulation 1049/2001, for cases "*where the decision has not been taken by the institution (...) if disclosure of the document would seriously undermine the institution's decision-making process*". During the same period, the French drug regulatory agency sent us three reports of bladder cancer, and a study by France's health insurance system confirmed a small risk of developing bladder cancer associated with this drug (25). The EMA's review of *pioglitazone* took nine months, from March to December 2011, during which time Prescrire was unable to access the reports collected by the EMA (26,27).

The EMA also refused, on the grounds of an ongoing referral procedure, to send us reports related to a review of the life-threatening risks of the *dextropropoxyphene + paracetamol* combination (Di-Antalvic°), one of the subjects of our 2010 complaints. In 2013, in response to our complaint, the European Ombudsman considered that disclosing these reports might "*put undue pressure*" on the EMA and the European Commission (8,15). At the time of our complaint in 2010, the evaluation had already been underway for 400 days (15). It took 800 days to complete (15). In its reaction to the complaint, the EMA failed to demonstrate how it was reasonably foreseeable that disclosure of these reports to Prescrire would have seriously undermined its evaluation (9). And in fact, by taking so long to complete its review (more than two years), it allowed concerns to emerge over whether the Agency carries out its duties entirely independently and in the public interest.

Also in 2011, a Cochrane review group asked the EMA for clinical study reports on *oseltamivir* (Tamiflu°) so that they could be taken into account in a systematic review the group was conducting. These researchers wanted access to the marketing authorisation documents because they had identified methodological bias in published articles and differences between the positions of the EMA and the

*Correction made after the issue was printed.

US Food and Drug Administration (FDA). The reports they received were incomplete: in particular, the anonymised individual case report forms describing adverse effects were missing (28,29).

In another example, the EMA refused our request for the first PSUR on *fingolimod* (Gilenya®) after the FDA announced in 2011 that a patient had died 24 hours after the first dose. Again, it cited an ongoing review as grounds for its refusal, which according to our calculations had begun 34 minutes before its deadline for responding to our application (30).

Legal action by drug companies opposed to disclosure

The EMA's 2011 transparency policy (Policy 0043) offered hope that the Agency would provide wide access to clinical data from marketing authorisations, in particular clinical study reports (14). But disagreements between the EMA and pharmaceutical companies over some or all of the reports disclosed have sometimes ended up before the European courts (31,32). These disputes have made the EMA less transparent, at least in its dealings with Prescrire.

Settled out of court at the expense of transparency. In April 2013, as part of a challenge brought against the EMA by the pharmaceutical company AbbVie, an urgent ruling issued by the EU General Court judge blocked the disclosure of a clinical study report on *adalimumab* (Humira®). This was a temporary measure pending a decision on the substance of the case (**c**)(33). The EMA appealed against this decision and, seven months later, the EU Court of Justice ruled in the EMA's favour. But in the meantime, the EMA had come to an agreement with AbbVie over a redacted version of the report, ending both the dispute and the prospect of a decision on the substance of the case, which would have set a legal precedent (31). AbbVie launched this legal action a few months after the EMA announced its intention to publish clinical study reports spontaneously (33).

2020: first major decision by the European Court of Justice in support of the disclosure of clinical study reports. Other legal challenges ensued. The most significant one began in 2015, when the marketing authorisation holder for *ataluren* (Translarna®), PTC Therapeutics, asked the European General Court to overturn the EMA's decision to disclose the phase 2 clinical study report on this drug to another company. This report was part of the marketing authorisation documentation held by the EMA. PTC Therapeutics wanted the court to recognise that this clinical study report was by nature confidential, meaning that the report in its entirety was confidential. The General Court rejected the company's view in 2018, as did the European Court of Justice in 2020 (31,32,34).

The European Court of Justice's judgment on the PTC Therapeutics case set an important precedent because it ruled as a court of cassation, i.e. on the interpretation of EU law. But vigilance is still required. When the General Court opposed the EMA's decision to disclose the clinical study report on *ataluren* in 2015, granting urgent interim relief to PTC Therapeutics, the EMA appealed against the decision, but was unsuccessful. The Agency had to wait for the court's decision on the substance of the case. And in 2019, in the appeal PTC Therapeutics brought before the Court of Justice, the Advocate General (whose role is to offer an independent legal opinion to judges of the European General Court or the European Court of Justice) upheld the general presumption of confidentiality for clinical study reports, on the grounds that their disclosure would be of considerable advantage to competitors (31,32,34). Prescrire and 42 international organisations drew attention across Europe to the danger that a victory for the company would represent (34). Remarkably, the European Court of Justice did not follow the Advocate General's advisory opinion, and instead concluded that the report was releasable, especially since certain data of a commercial nature had been redacted (31). However, the Court of Justice did not firmly recognise that, as a general principle, clinical study reports cannot be presumed to be confidential in their entirety (32).

Negative impact of litigation on responses to Prescrire's requests

The cases brought before the European General Court by pharmaceutical companies in order to prevent the EMA from disclosing clinical study reports negatively affected its responses to Prescrire's requests for several months.

The cases of cefuroxime and defibrotide. In July 2013, with AbbVie's case against the EMA before the European General Court, the EMA refused to send Prescrire documents on the European harmonisation of marketing authorisations for medicines containing *cefuroxime* (35). We had requested two reports, including the clinical overview produced by the pharmaceutical company, which is a key document in harmonisation procedures (22). During the same period, the EMA refused to send us packaging mock-ups for a different drug, then relented when we requested them a second time (36).

The EMA cited the ongoing legal proceedings before the General Court as its reason for refusing these requests (35). Yet these documents were unrelated to AbbVie's case. When the EMA confirmed its refusal to send us the reports on *cefuroxime*, we requested and subsequently received them from GlaxoSmithKline, the marketing authorisation holder for the *cefuroxime*-containing product Zinnat® (22).

c- *When a case falls under the jurisdiction of the General Court of the European Union, its role is that of a lower court. Appeals against its decisions can be brought before the Court of Justice of the European Union. In interim proceedings, the General Court can urgently order provisional measures while awaiting a ruling on the substance of the case, which may or may not uphold the interim measures (ref 61).*

In July 2014, the EMA refused to send us a clinical study report on *defibrotide* (Defitelio®), but eventually obliged, having asked Prescrire in the meantime to justify our request (20,37).

The case of ataluren. In 2017, we asked the EMA for the phase 3 clinical study report on *ataluren*, due to major weaknesses in its evaluation (38,39). With the PTC Therapeutics case over the disclosure of the phase 2 clinical study report in full swing, the EMA implied in its response that fulfilling our request might jeopardise the chances of obtaining a ruling from the General Court "*confirming that clinical study reports should be made public*" (38). This response, which was not an official refusal, meant that Prescrire could not repeat its request. Yet it was unlikely that the court would have opposed the disclosure of a clinical study report in principle, given that the 2014 Clinical Trials Regulation requires their publication by the EMA (more on this later) (38). The EMA knows that applicants cannot lodge a complaint with the European Ombudsman unless the institution to which they applied for access to a document has refused twice (40,41). We sent a second application anyway, to which the EMA's response more clearly resembled a refusal (38).

Negative impact of litigation on EMA's proactive transparency. Unsurprisingly, these legal proceedings also had a negative impact on the EMA's proactive transparency policy (see "The European Medicines Agency's "proactive" transparency" pages 136-137).

In 2018, we searched the EMA website for the main reports on the clinical evaluation data submitted to obtain marketing authorisation for *migalastat* (Galafold®). No documents were available on the website, and a message had been posted explaining that this was because the drug's marketing authorisation holder, Amicus Therapeutics, had filed an action with the European General Court to prevent the disclosure of a clinical study report (42). In this case too, the company was arguing for a general presumption of confidentiality for clinical study reports, claiming that by their very nature they are confidential in their entirety. The General Court rightly considered that the requirement for the EMA to publish clinical study reports, established in the 2014 Clinical Trials Regulation, was incontrovertible evidence that there is no general presumption of confidentiality regarding such documents (31).

International agreements on industrial property complicate matters

Article 39 of the agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), an annex of the 1994 agreements establishing the World Trade Organization (WTO), concerns marketing authorisations for new drugs. It stipulates that WTO member states shall protect "*undisclosed test or other data, the origination of which involves a considerable effort (…) against unfair commercial use*", when companies submitted such data to obtain marketing authorisation (43). Unlike in European law, where transparency is the rule, the international agreement on industrial property rights makes disclosure an exception: "*Members* [who have signed the agreement] *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*" (43). The latter protection exists in effect in the EU, because clinical data provided in support of marketing authorisation applications are protected from competition from generic manufacturers for 8 years, followed by an additional 2 or 3 years of market exclusivity (31).

The purpose of Prescrire's applications for access to these data is to protect the public, an exception provided for in the TRIPS agreement.

Counterproductive procedures imposed by the EMA since 2015

According to European Regulation 1049/2001, "*an application for access to a document shall be handled promptly (…) within 15 working days from registration of the application (…). In exceptional cases, for example in the event of an application relating to a very long document or to a very large number of documents, the time-limit (…) may be extended by 15 working days, provided that the applicant is notified in advance and that detailed reasons are given*" (3).

The EMA started handling requests in new ways as of 2015.

Drug companies given 10 days to bring legal action before disclosure of a document that concerns them. According to Regulation 1049/2001, when access is requested to a "*third-party*" document held by an institution, i.e. a document that the institution did not produce but received from an entity outside the institution, such as a PSUR submitted to the EMA by a pharmaceutical company, "*the institution shall consult the third party with a view to assessing whether an exception* [to the right of access] *(…) is applicable, unless it is clear that the document shall or shall not be disclosed*" (3).

According to the EMA (our translation), "*the principle of access to justice includes the right of third parties to request a judicial review (by the Court of Justice of the European Union) of the EMA's decision to disclose the document or documents, before they are actually sent to the applicant*" (44). The EMA therefore grants pharmaceutical companies a period of 10 working days to institute legal proceedings. Judging by the responses we receive from the EMA, this period appears to be granted almost systematically (44).

In our view, the 10-day delay that the EMA offers pharmaceutical companies is excessively generous (24). In practice, it is also applied to documents produced by the EMA itself, for example the PRAC's report on *selexipag* (45). The EMA also applies it to

scans of packaging items that Prescrire requests, including the box, labelling and patient leaflet of medicinal products manufactured in EU member states (24,46). The overcautiousness the EMA exhibits with regard to pharmaceutical companies is more general: for example, it gets them to review European Public Assessment Reports (EPARs) before publishing them on its website (47). EPARs are written on the basis of reports produced by national drug regulatory agencies, but are a highly condensed and already cautious summary of the various modules that make up the marketing authorisation application (5).

Queuing system for requests: 91 days to send 11 pages. Beginning in 2015, the EMA gradually introduced a queuing system for requests. A new request from a given applicant can only be registered once the previous one has been fully processed and closed, which can take 3 or 4 months. The statutory 15-day time limit, stipulated in Regulation 1049/2001, within which European institutions must respond to applications for access to documents, only starts at this point (44). While this regulation states that requests should be handled "within 15 working days from registration", it previously establishes that "*an application for access to a document shall be handled promptly*", a requirement that the queuing system clearly fails to meet (3).

We shall illustrate the situation with a single example, and have deliberately chosen a very small document. The EMA received a request from Prescrire on 13 February 2019 for packaging items for *glycerol phenylbutyrate* (Ravicti®). Applying its queuing system, the EMA started processing our request 3 months after receiving it, on 17 May 2019, once our previous request had been closed. It sent us the document on 27 June 2019. A total of 91 working days therefore elapsed between submission of our request and receipt of the document (46). But the EMA considered it had processed our request within 16 days. It had subtracted the 65-day delay before it began to process our request and the 10 days allowed for pharmaceutical companies to institute legal proceedings (44). These new procedures considerably increase the time it takes to obtain information and, in this example, we had simply requested an 11-page scan of the German packaging for Ravicti®, consisting of a box, bottle label and patient leaflet (46). And the EMA already had these items in its possession in order to examine the drug's packaging before its market introduction (48).

Batch release: a single application holds up others for several months. Some of the large documents, such as PSURs, sent to us by the EMA have been released in several batches and took more than 30 days, a process the EMA introduced in violation of Regulation 1049/2001 (44,49). In 2014, two PSURs on HPV vaccines (Cervarix®, Gardasil®) were received in 3 batches over a period of 3 months (50). We considered this delay acceptable, however, given that these documents amounted to almost 5000 pages.

The EMA then started releasing much smaller requests in batches. In 2019, we requested 5 documents: a PRAC report and PSURs on *pentoxyverine* from four pharmaceutical companies. The EMA began processing our request after one month, and the documents were gradually released in 5 batches over a period of 8 months (51). None of our other requests were admissible during these 8 months, because of the queuing system. We received a total of 200 pages during this period, as compared with nearly 5000 pages in 3 months in 2014 (52).

Ombudsman's decisions were behind tougher procedures for access to documents, according to the EMA

The European Ombudsman's decision in 2010, based on European law and robust case-law in favour of wide access to data from marketing authorisation applications, was a positive factor in the EMA's decision to be more transparent from 2011 onwards (12). But two subsequent decisions by the Ombudsman had negative effects (49,53).

Disclosure of the identity of applicants to drug companies. In 2015, a company asked the EMA for a document submitted by another company (which, for the sake of clarity, we will refer to as company B). Company B asked the EMA to disclose the identity of the applicant (company A). The EMA refused, in order to protect the applicant's commercial interests. Company B filed a complaint with the European Ombudsman about the EMA's decision: it wanted to know the applicant's identity, based on the assumption that it could be a future competitor (53).

In July 2017, the Ombudsman found that the EMA's systematic refusal to disclose the identity of organisations that request access to documents constituted maladministration. The Ombudsman rejected the EMA's argument that its procedure applied regardless of the nature of the applicant, and took the position that the applicant might indeed be a current or future competitor of company B. The Ombudsman recommended that, when a company requests access to documents, the EMA should check with this company how the disclosure of its identity might undermine its commercial interests (53).

Decision on the queuing system. In 2017, a journalist filed a complaint with the European Ombudsman against the EMA for maladministration. The journalist felt that the EMA was using the queuing system, and the resulting increase in response times, as a deterrent, and was favouring the pharmaceutical industry. He claimed that the EMA's procedures caused it to take much longer to respond to requests, with the knock-on effect that applicants would choose to submit fewer requests. He argued that it was the EMA's responsibility to employ sufficient staff to deal with the requests it receives, rather than the responsibility of applicants to adapt to the EMA (49).

The European Medicines Agency's "proactive" transparency: embracing transparency or avoiding litigation?

The data which the European Medicines Agency (EMA) publishes in order to comply with European regulations on drugs, in documents such as European Public Assessment Reports (EPARs), are just the tip of the iceberg in terms of the vast quantities of data in its possession (1,2). These documents are produced through standardised procedures with checks along the way (3,4). EPARs are highly summarised overviews of marketing authorisation applications, in which the tens of thousands of pages of documents that pharmaceutical companies are required to submit to the EMA are condensed into only 100 to 200 pages (1,3). They are also based on unpublished assessment reports produced by the national drug regulatory agencies of European Union countries (referred to as rapporteurs and co-rapporteurs) tasked with evaluating applications, on which the EMA relies heavily when preparing its own reports (2).

Similar rules apply to "variations", i.e. applications to modify an existing marketing authorisation, for example to add a new adverse effect. Limited information is made public about variations too, as neither drug company documents nor the EMA's assessment reports are published. Examples of useful yet unpublished documents include: drug companies' Periodic Safety Update Reports (PSURs), containing pharmacovigilance data; the assessment reports produced by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) on these PSURs; the PRAC's reports on the first cases of a probable new adverse effect (or "safety signal"); and reports produced by the EMA's Committee for Medicinal Products for Human use (CHMP), for example on paediatric extensions (see "European Medicines Agency: transparency policy marred" p. 130-139).

As a European institution, the EMA is required by European regulations to provide access to the documents in its possession "*as far as possible (...) in electronic form or through a register* (...)" (5). In practice, it is supposed to spontaneously publish a selection of the many documents containing clinical data on which it bases its recommendations. It was in this spirit that the EMA proposed its "proactive" transparency policy (Policy 0070) in 2014 (2).

2016-2018: publication of marketing authorisation documents and censorship, mainly information about adverse effects. In October 2016, four years after a broad public consultation, the EMA began publishing large quantities of clinical data on its website (6). These data, produced by pharmaceutical companies, came from mandatory sections of marketing authorisation applications, including clinical study reports.

The EMA published documents on 141 procedures between 2017 and 2018, three-quarters of which were applications for the authorisation of new drug substances, new indications or new dose strengths of existing drugs (7). This transparency at the EMA must be weighed against a major setback: the announcement that implementation of the 2014 Clinical Trials Regulation would be delayed until 2022. This regulation sets out the procedures for obtaining marketing authorisation and conducting clinical trials in the European Union. It included a number of advances in transparency, requiring the EMA to publish clinical study reports once marketing authorisation has been granted, via a publicly accessible database maintained and controlled by the EMA (6,8).

The public database went live in late January 2022, but we fear that the transparency requirements set out in this regulation will be undermined (8,9). A 2015 report by the European Parliament pointed out the fact that the EMA's policy on the proactive publication of marketing authorisation documents (Policy 0070) included allowing pharmaceutical companies to redact any data they consider commercially sensitive (10).

Covid-19, selective transparency. In the clinical overview of the marketing authorisation for the covid-19 vaccine *tozinameran* (Comirnaty®), published online in December 2020, one-third of its 257 pages had been heavily redacted, as had almost half of the 2000 pages of a clinical study report on this vaccine (11,12). Most of the chapters that had been redacted concerned adverse effects or the reasons patients left the trial (11,12). The redacted parts are marked "interim results of an ongoing trial impacting study blinding" (11,12). The EMA, which we queried in September 2021, considers that publishing these interim results might bias the ongoing trial (13). But if that were the case, why are the only data redacted those on adverse effects?

The documents that form the basis of conditional marketing authorisations invariably contain incomplete data (as in the case of the covid-19 vaccines authorised in the European Union, such as *tozinameran*), yet decisions are made and cases are closed on the basis of such data, as pointed out by the judge in a case brought before the European courts by a pharmaceutical company that objected to the EMA disclosing such a document (14). We therefore see no valid reason why conditional marketing authorisations should be an exception to the requirement for access to clinical data. In another example, more than half of an almost 26 000-page clinical study report on *empagliflozin* (Jardiance®) had been redacted (15).

Criticised by MEPs. Members of the European Parliament (MEPs) interpreted the EMA's policy of allowing pharmaceutical companies to redact clinical study reports as part of its "proactive transparency" as an infringement of the transparency provisions of the 2014 Clinical Trials Regulation (10). This regulation requires that the EMA publish clinical study reports once marketing authorisation has been granted, with no suggestion that the censorship of clinical data is permissible (8).

The EMA paused its publication of clinical modules from marketing authorisation applications in late 2018, apart from those for drugs used in covid-19 (7). The reason given by the EMA was its increased workload due to its move from London to Amsterdam (16).

Proactive transparency after authorisation: insufficient. Marketing authorisations are granted more and more rapidly, on the basis of insufficient evidence and a promise to conduct post-authorisation studies (17). Proactive transparency over post-authorisation decisions is therefore crucial. But in practice, the EMA publishes very little of the data on which its post-authorisation recommendations are based, especially data on adverse effects. The raw data on adverse effects published in its public database ADRreports (www.adrreports.eu) have their uses, but are difficult to use and of limited value in an evaluation, because insufficient information is provided, for example, about any other factors that could have contributed to the adverse effect (18).

When the first cases of a potential new adverse effect are reported, the PRAC only shares a few lines of information, as was the case in 2017 following a death linked to *selexipag* (Uptravi®), despite the existence of a 79-page internal document containing detailed information about *selexipag*-related deaths, the company's responses to the PRAC's questions, and the PRAC's analyses during the course of the evaluation (19,20). We became aware of this on reading this report, which we received with only slight redactions. The PRAC produces many similar reports.

The CHMP also produces numerous assessment reports on major variations to marketing authorisations, which are not published. For example, the authorisation of *duloxetine* (Cymbalta®) was extended to include children with generalised anxiety disorder through a simple change to the "Posology" section of its summary of product characteristics (SPC). Such changes do not usually lead to the release of a detailed report, yet a 38-page report on it was tucked away in a "drawer" at the EMA (21,22).

As of early 2022, the EMA's default position on post-authorisation data is to withhold them; transparency is the exception. This policy runs counter to the Agency's transparency obligations and the need to confirm or revoke marketing authorisations that were granted on the basis of insufficient preliminary data. As regards proactive transparency over data associated with new marketing authorisations, the EMA must show that its policy is in line with the need to keep patients safe, rather than pretending to be transparent while allowing pharmaceutical companies to hide clinical data they consider to be a threat to their commercial interests.

► Translated from *Rev Prescrire* February 2022 Volume 42 N° 460 • Pages 143-144

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The European Ombudsman found no maladministration in a 2019 decision regarding this complaint. The Ombudsman pointed out that the EMA allows applicants to prioritise certain requests, and stated that not only there was no favouritism shown toward pharmaceutical companies, but that they are the most affected by longer delays because they submit the most access-to-document requests. In addition, the journalist had obtained 63 responses in 15 months and, according to the Ombudsman, had probably used unfair means by getting third parties to submit requests on his behalf (49).

Prescrire indirectly penalised by the Ombudsman's decisions. The EMA explained to the European Ombudsman in 2015 that it was willing to keep the identity of applicants confidential. However, in 2013, it started asking us whether it could disclose our identity to pharmaceutical companies, explaining that it would only do so with our consent and that we were not obliged to give our reasons (54). We refused to consent to the disclosure of our identity.

The EMA became more insistent, and we expressed our concern in mid-2014 in a letter that we also sent to the European Ombudsman. We pointed out how unsurprising it was that pharmaceutical companies

*Correction made after the issue was printed.

would seek information on applicants, citing examples of companies using intimidation tactics, such as when Merck Sharp & Dohme (MSD) forced an Italian doctor to remove an article from his website about the cholesterol-lowering drug *ezetimibe* (54). The EMA disclosed the identity of Prescrire for a while, blaming a technical mix-up. And a pharmaceutical company phoned a member of our editorial staff, requesting justification for one of our requests (55).

The EMA gets tough with Prescrire. Beginning in 2014, the EMA started asking Prescrire to justify its objection to disclosure of its identity (55). It then took a tougher stance, citing the European Ombudsman's recommendation in 2017 that the EMA review its policy of refusing to disclose the identity of applicants. It was no longer a matter of us giving or refusing our consent for the EMA to disclose our identity. Once, when a pharmaceutical company had asked for our identity to be disclosed, the EMA sent us a document it had prepared, in which a copy of our request had been inserted among administrative information (the identity of the EMA agent who had processed the request, processing steps). Some of the data in this document had been redacted, including those relating to the EMA's administrative procedure, but the name "*Prescrire*" had been left unredacted (56). We were simply asked to accept these redactions or to suggest changes to them.

After the European Ombudsman's 2019 decision on the queuing system, the EMA made its procedure even more restrictive, including the introduction of a limit of two documents per request (57). Little by little, Prescrire saw response times increase even more. The queuing system, batch release and the 10-day period granted to pharmaceutical companies to institute legal proceedings became systematic, each adding further delay.

As of early 2022, these procedures mean that Prescrire can hope to receive, in a year, just one response from the EMA to an application it considers large (about 200 pages) and six scans of packaging items (about 10 pages each). As for the option of prioritising requests, as mentioned by the European Ombudsman, it proved counterproductive for Prescrire. When faced with response times of several months, there is little point in prioritising one specific request, when this may just delay news on other requests still further.

Prescrire's list of unanswered requests grew longer. Mindful of the need to inform the healthcare professionals who subscribe to *La Revue Prescrire*, and seeing no prospect of obtaining a timely response from the EMA, we retracted several requests (24). The queuing system prevented us from following up with the EMA once the statutory 15-day deadline imposed by Regulation 1049/2001 had expired. Through this procedure, the EMA avoids issuing official refusals, thus preventing applicants from submitting a complaint to the European Ombudsman, which induces self-censorship among applicants.

In summary: to unblock transparency and end ambiguity at the EMA, an official inquiry for submission to the European Parliament is needed

In late 2010, the EMA embarked on a transparency policy consistent with the high standards of transparency required within the EU. The obstacles observed over the years raise doubts over its commitment to providing full access to the clinical data contained in marketing authorisation applications. Its cautious reactions suggest genuine fear of the legal action brought by pharmaceutical companies.

Transparency is supposed to be the default position for EU institutions, and non-disclosure the exception. The restrictions imposed by the EMA over time on access-to-document requests especially penalise researchers, non-profit organisations, the public and patients, yet the congestion within the system is due to the drug companies and consultancies that submit 70% of the requests and have the means to intimidate and litigate (58).

Two decisions issued by the current European Ombudsman, which seem to have set a precedent in the eyes of the EMA, have had a negative impact on Prescrire's requests. We are unconvinced by the European Ombudsman's decision to accept the EMA's argument that it can refuse to release documents because a European review is in progress.

The EMA's unusual circumstances of relocating from London to Amsterdam because of Brexit, then dealing with the covid-19 pandemic, do not alter our view. The obvious failings of the EMA's access-to-documents service justify an official inquiry so that Members of the European Parliament can take appropriate steps: the EMA's interpretation of exceptions to disclosure should be subjected to legal analysis; more resources must be allocated to implementing the right of access to documents; the specific needs of applicants with no profit motive (such as Prescrire) must be taken into account; and the EMA must be inspected and called to order if it censors clinical data.

The European Parliament and the European Commission, which are responsible for adherence to the institutional and regulatory principles of the EU, should also ensure that clinical study reports are published in their entirety, as required by the Clinical Trials Regulation.

We will have more on this topic in a future issue.

Review produced collectively by the Editorial Staff: no conflicts of interest

► Translated from *Rev Prescrire* February 2022 Volume 42 N° 460 • Pages 136-146

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