Europe's opportunity to open up drug regulation

Among the priorities for the European health directorate, DG Sanco, as it takes control of the agency in charge of drug regulation should be to end the secrecy surrounding approval decisions, say **Silvio Garattini** and **Vittorio Bertele'**

Questions about the benefits of the flu drug oseltamivir in otherwise healthy people[1 2] have fuelled debate about the secrecy surrounding the documentation submitted for marketing authorisation of new medicines. Greater transparency would open drug dossiers to evaluation by the scientific community and help independent interested parties define the benefit-risk profile of new medicines before they are allowed on to the market. The recent movement of the European Medicines Agency (EMA) to the Health and Consumer Policy Directorate (DG Sanco) rather than the Enterprise and Industry Directorate presents an opportunity to introduce more openness.

The secrecy surrounding the dossiers presented by drug companies to obtain approval of new drugs has received little attention in Europe. Writing about the oseltamivir issue, Fiona Godlee states that "it is a legitimate scientific concern that data used to support important health policy strategies are held only by a commercial organisation and have not been subject to full external scrutiny and review."[1] This is important because a new drug authorised by the EMA can be marketed in all the European member states without further evaluation.

What we know about new drugs

EMA releases four documents when a new drug is approved

- A press release the day after the approval containing only general information
- The summary of product characteristics—a technical file intended for prescribers
- A leaflet that is inserted in the drug package for patients' information, and
- The European public assessment report (EPAR), which summarises the documentation produced by the manufacturer and the procedures that have led the Committee for Human Medicinal Products to approve the new drug.

Except for the press release, all these documents are written in close collaboration with the manufacturer.

What is missing?

The summary of product characteristics does not mention when a drug is approved by majority vote, and the European assessment report does not give the reasons for the minority's opposition. Summaries of product characteristics describe single drugs, whereas they should really compare them with other drugs with similar mechanisms of action or intended for the same indications. Comparative information would show whether differences in efficacy or safety are clinically important and whether responses to a product by patients resistant to a different one are thoroughly documented.

The European public assessment report does not reflect the critical issues that the committee examined and discussed during assessment. It also does not contain the initial reports submitted by the rapporteurs (two members of the committee who prepare a preliminary assessment report for the committee to discuss and approve) or the manufacturer's replies to the questions raised. This information could clarify how the final decision was reached.

Finally, the EMA cannot release any original document that the manufacturer submits for the approval process. However, in the United States the Food and Drug Administration can, under given conditions, make at least substantial parts of the original documentation available to scientists, clinicians, or patients' representatives.

Reasons for secrecy

Why does the European legislation uphold this secrecy? One reason is that until recently the EMA reported to the Directorate General of Industry and Enterprise. The industry considers it has the right to secrecy, in order to protect the substantial investments made to develop a new drug. Any disclosure of data could give competitors an advantage and damage industrial interest and profits. Any loss of profits could reduce investment in research so in the end it will create a disadvantage for patients too, who will have fewer drugs.[3]

Arguments for greater transparency

This reasoning can be challenged because the drug industry is not the sole financer of research. It draws on the results of all the laboratory and clinical studies carried out by academic institutions worldwide supported by public money. Furthermore, clinical trials require the participation of patients, who take part free of charge. Finally, in most European countries the drug market is prosperous because it is guaranteed by national health services. The public is thus not only a beneficiary of new discoveries but also an essential partner. It therefore has the right of access to all relevant information. Secrecy about clinical data implies undue exploitation of the rights of doctors and patients participating in the studies.[4]

Industry's concern about disclosing informa-

Comparison of the European and US regulatory systems

	EU (EMA)	US (FDA)
Register of ongoing and completed clinical trials	Not accessible	Accessible
Drug information held by agency	Not accessible	Accessible according to Freedom of Information Act
Records of meetings with industry	Not available	Available
Minutes of advisory committee meetings	Not available	Available
Statements of the minority	Not available	Available
Proportion of agency's budget covered by industry	About 70%[6]	About 20%[7]

tion that may be useful to competitors is understandable. However, it is important to make a distinction: secrecy may be justifiable for information about the production of the active ingredients and the methods used for drug discovery; but preclinical findings, particularly toxicological studies, and clinical controlled trials are unlikely to be important for the competition. Since these data will have to be disclosed for all new products, in the long run advantages and disadvantages will be equally distributed.

How the European health directorate could improve drug regulation

- More rigorous evidence of efficacy—all drugs should have proved benefit in studies that use clinical end points over an adequate length of time
- Greater transparency about evidence used to make decisions
- Establish a European-wide network for post-marketing pharmacovigilance to detect signals of toxicity[12] or lack of efficacy[2]—the results should be evaluated by a different body from that which granted the marketing authorisation, which might feel bound by its previous decision
- Newly approved medicines should have better efficacy or safety than available ones
- The European Commission should fund independent studies to support data produced by drug companies and explore further clinical potential of drugs with no commercial appeal but public health value[4]
- The EC should cover the EMA budget so that it is not reliant on the fees paid by drug companies

It is also difficult to see why the EMA cannot provide the same access to information as the FDA (table).[5] The abolition of confidentiality would help make the system more transparent and enable clinicians and patients' representatives to obtain information on which to base constructive criticism, establishing public confidence and improving research in the industry itself.

Transparency as a means to avoid bias

Transparency of the regulatory system is also required to overcome several dysfunctions in the drug industry's behaviour. As with oseltamivir,[1] positive results are more likely to be published than negative ones.[8 9] For instance, the fact that the FDA has made available all the results of trials concerning selective serotonin reuptake inhibitors—published and unpublished—has considerably weakened the importance of this class of antidepressants.[10]

Greater transparency will also cast light on deviations from trial protocols, which have often been reported in the independent literature.[11] This will have the advantage of providing reliable data for meta-analysis, systematic reviews, and guidelines.[11] Furthermore, for pharmacoeconomic evaluations to be reliable, they need access to the original clinical data, not just abstracts or articles. Last but not least, it is important to underline the responsibility of academic institutions and clinicians who agree to perform studies without being allowed to contribute to the evaluation and interpretation of the results. If data were publicly available, the investigators would be more critical about granting their authorship.

Need for change

Some changes are required to make sure that the final aim of information related to drugs is oriented to the interests of patients (box). This involves a two way approach: industry should provide the agency with all the relevant data it holds; the EMA should provide more information on how the evaluation criteria are applied in the single assessment procedures. European legislation should establish that, at least, the results of toxicological tests and clinical trials are not to be kept confidential. Access to drug dossiers by the scientific community and the public would make it harder for companies to hide unfavourable data. To make EMA's procedures more transparent, the original data, the rapporteurs' initial reports, the discussion between the Committee for Human Medicinal Products and industry, and the minority opinions should all be accessible. Abolition of secrecy by EMA would boost the regulatory authorities' credibility and show that patients' health has priority over industrial interests.

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