How can we regulate medicines better?

Current European licensing regulations give precedence to the interests of drug companies.

Silvio Garattini and **Vittorio Bertele'** suggest changes to ensure they meet the needs of patients and doctors

Despite the undoubted advantages of the establishment of the European Medicines Agency (EMA)^{w1} criticisms have been made, mostly about its independence and transparency and the evaluation criteria.¹⁻³ The 2004 European Commission law expanded the agency's remit but did not significantly change the methods of regulation.^{w2} We offer a few proposals aimed at bettering the work of the agency. These may require important changes in current law regulating the pharmaceutical system.

Agency's role

The agency gives opinions on the quality, safety, and efficacy of new drugs that manufacturers want to market in the European Union. The European Commission uses the agency's opinions to decide whether to grant a licence.

Unlike the US Food and Drug Administration, the European agency is not autonomous but an expression of the national agencies in the European Union, which approve most new products. Evaluation through the centralised procedure has become mandatory for biotechnology products and drugs for HIV, cancer, neurovegetative disorders, diabetes, rare diseases, the autoimmune system, and viral diseases. The European agency is important because central authorisation is increasing and because national agencies cannot justify adopting methods and criteria inconsistent with those of the central agency. When national agencies come to differing decisions, the European agency makes a final decision that is binding in all member states.

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Accepted: 16 June 2007

Added value of new drugs

Too many drugs are approved on the basis of surrogate end points that are not validated predictors of therapeutic end points. Numerous cancer treatments have been authorised on the basis of tumour response that is not correlated with an improvement in quality or duration of life.⁴ Manufacturers often object that it would take too long to prove a therapeutic benefit and that patients should not be denied potentially useful drugs, particularly for severe diseases. Assuming this is a valid objection, it is still unclear why drugs in the same class have sometimes been authorised before the therapeutic efficacy of the first drug approved has been shown, as was the case with drugs for pulmonary hypertension and HIV and glitazones for diabetes.

Drug companies sometimes do long term post-marketing trials with hard end points in order to define the new drug's efficacy in relation to available alternatives. However, doctors and patients need to know relative efficacy at the time of approval if they are to make objective decisions about drugs. Moreover, commitments to new studies are seldom fulfilled,^{w3} the excuse being that since the product has been approved no doctor wants to randomise and no patient wants to be randomised to placebo or an active comparator. Marketing approval is perceived as the recognition of an added value, even though this is often lacking.

New drugs have only to show they are of good quality, effective, and safe, independently of any reference or comparison to drugs already on the market. This results in overuse of trials against placebo. Even when new drugs are compared with existing treatments, the trials often seek to show equivalence or non-inferiority rather than superiority to those already available. Such trials could allow drugs into the market that are less active or safe than those in current clinical use. This is because the non-inferiority limit includes a higher incidence of adverse events. The wider the limits the smaller the sample needed and consequently the higher the chance of missing a difference and concluding for non-inferiority. Sometimes limits are so wide that what is considered non-inferior statistically may be worse clinically.^{w4 w5}

Non-inferiority trials clearly aim at overlooking differences that might preclude entry to the market rather than highlighting them.⁵ This tendency occurred even before non-inferiority trials came into use. In a survey of 383 clinical trials testing superiority in major clinical journals, only 16% of the 70 trials with negative results had sufficient power (80%) to detect a 25% difference and only 36% had power to detect a 50% difference.⁶

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Only 3% of trials in schizophrenia had enough power to show a 20% improvement in mental state.⁷ It is easier to get to the market by proving a new product is similar to standard available treatments than by failing to show it is superior.

It is unethical to experiment on patients with the sole aim of obtaining a marketing authorisation. New drugs should be required to have some added value (greater efficacy or less toxicity) to current treatments or be cheaper. The FDA is apparently changing its mind on the suitability of non-inferiority trials,^{w6} and we hope the EMEA will follow the same path.

Independent research and development

At present, manufacturers prepare the reports seeking approval for a new drug or a new indication. Companies will clearly tend to maximise the benefits and minimise the risk. The expert opinion that accompanies the research reflects this. Industry sponsored research is more favourable to new products than research done by non-profit organisations,⁸ as shown by trials on multiple myeloma, schizophrenia, erythropoietin, and mycophenolate mofetil.^{w7-w10} Authors' conclusions in randomised clinical trials were significantly more likely to favour experimental interventions if they declared financial competing interests.⁸ Study protocols are developed to favour new drugs: industry prefers to use placebo or no therapy as comparator more often than non-commercial sponsors.^{w7}

One way to overcome this problem would be to introduce some element of independent research by a non-profit organisation.⁹⁻¹² For example, the regulatory agency could require one phase III trial (usually two pivotal trials are needed) to be planned and carried out by an independent organisation credited by the agency, particularly for drugs that are going to be reimbursed by national health services. Independent research should also aim at developing new drugs for conditions that might not be attractive to commercial companies, such as treatments for rare diseases. In such cases the EMEA could commission a study by academic health structures, which would be audited by independent research organisations.

At present independent research occurs only after approval. The Italian regulatory agency, for example, requires drug companies to contribute 5% of their promotional expenses each year, which it uses to fund research.^{w11} Funds are allocated according to a priority score established by discussion groups including international reviewers, and the projects range from trials to optimise the use of orphan drugs to comparison of drugs licensed for the same indications and observational studies dealing with pharmacovigilance. This initiative could be extended to the premarketing phase and coordinated at the European level.

Disclosure of drug information

Another concern with the European agency is transparency. Unlike the FDA, the EMEA keeps almost all its information secret.^{w12} Although disclosure of documentation concerning production and drug tech-

nology could help competitors, there is no reason to hide data on toxicology and clinical evaluation.^{13 14} This information is essential to understand why a new drug has been approved or a new indication granted. Although the agency releases a European public assessment report, this is a generic document written under the supervision of the company concerned.

Other information that should be made transparent includes the size of the majority that approved a given drug, the reasons of the minority for opposing approval, conflicts of interest, and post-marketing commitments and their fulfilment. When drugs are approved "under exceptional circumstances" on evidence from surrogate end points, the manufacturers usually have to commit to do further research. However, in many cases they ask for extra time or do not meet the commitment at all. A recent FDA survey indicated that only 926 (34%) out of 2701 post-marketing commitments were honoured.^{w3} No equivalent information is available from the EMEA.

The documents made available by the EMEA do not disclose the issues raised in the evaluation of marketing application, do not reflect the debate in the Committee for Human Medicinal Products (the body that gives the European Commission opinions on new drugs), and therefore do not allow an independent evaluation by people outside the agency.

Implementing active pharmacovigilance

One important weakness of the European drug system is pharmacovigilance. It relies on national activities, which in several cases are limited to spontaneous reports from patients and doctors. Clearly, collection of data about drug toxicity could be strengthened by establishing a network covering all 25 European countries, coordinated by the EMEA. The establishment of EudraVigilance in 2001 was intended to facilitate this, but the system is still far from being fully implemented. EudraVigilance is a data processing network aimed at facilitating the electronic exchange of suspected adverse reaction reports between the European agency, national authorities, marketing authorisation holders, and sponsors of clinical trials in Europe.

Proposed models for future pharmacovigilance include actively looking for toxicity rather than relying on spontaneous reporting.¹⁵ The proactive approach requires research projects to investigate severe adverse reactions such as gastrointestinal bleeding, prolonged Q-T interval, rhabdomyolysis, hepatitis, renal insufficiency, and dependence. Programmes should focus on the signs of toxicity for specific drugs or classes of drugs. In addition, companies should be obliged to present meta-analyses of both beneficial and adverse events in the regular safety update reports they submit to the EMEA.

The EMEA should establish a new pharmacovigilance committee, separate from the Committee for Human Medicinal Products.¹⁶⁻¹⁸ Decisions to restrict the use of a drug or to withdraw it from the market must be taken by an independent group devoted to pharmacovigilance. The medicinal products committee already has a heavy workload and may be unconsciously resistant to withdrawing a drug that it has approved.

Removal of bias

The current power of drug companies conflicts with the right of patients to receive drugs that have been studied enough to guarantee that they are more effective and safer than current treatments. Major international clinical journals have helped to make the influence of drug companies clearer by requiring that authors declare they know the content of the articles, avoiding ghost writing by people paid by drug companies^{w13}; state conflicts of interest^{w14}; and register protocols of clinical trials to highlight changes made after the trial has begun.^{w15}

The regulatory system is also subject to bias and suspicion. For instance, it is anomalous that the EMEA is part of the EU general directorate of enterprise and industry rather than the general directorate of health and consumers. It is also strange that the general directorate of enterprise regulates compliance to good clinical practice by non-profit organisations.^{w16} It is equally surprising that about 70% of the agency's budget comes from fees paid by the applicants.

Some of our suggestions will make the approval of new drugs and new indications more difficult and prolong the time needed for their introduction into the market. We may therefore need to be more flexible to encourage industrial research. One possibility would be to prolong product patents in exchange for better, safer, more trustworthy, and more affordable innovation.¹⁹ We believe the changes will not only be important for patients but will help stimulate innovative research by drug companies.

We thank Fernando de Andres Trelles for his help, Elena Gardinale and Davide Lauri for reviewing the paper, and J D Baggott for editorial help.

Competing interests: SG and VB are director and researcher at the Mario Negri Institute for Pharmacological Research, an independent

SUMMARY POINTS

Licensing of new drugs in Europe is increasingly controlled by the European Medicines Agency
Current regulations need changing to ensure all new drugs add value
Assessment should include a phase III study by an independent organisation
Toxicological and clinical information should be made public
The European pharmacovigilance system should be implemented

non-profit research institute devoted to patients' and national health services' interests. The Institute could take advantage of the proposal to increase the role of independent research in setting up the documentation supporting marketing authorization applications for new drugs or new clinical indications.

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CORRECTIONS AND CLARIFICATIONS

The future of the medical profession

The printers' devils were mixing up commas and apostrophes in this editorial by Roger Jones (*BMJ* 2007;335:53, 14 Jul). The final sentence of the third paragraph should read: "The role of doctors, careers in medicine, and the future of a publicly funded health service have all been questioned" not "The role of doctors' careers in medicine, and the future of a publicly funded service . . .".

Cardioversion of atrial fibrillation

An error has belatedly emerged in relation to this article by Gregory YH Lip and colleagues in the ABC of Atrial Fibrillation series (*BMJ* 1996;312:112-5). In the graph with the caption that reads "Patients in sinus rhythm at time of cardioversion and at one month and six months of follow up according to duration of atrial fibrillation" the labels for the blue and red bars are the wrong way round. The blue bars represent "less than 3 months" of atrial fibrillation not "more than 12 months" and the red bars represent "more than 12 months" of atrial fibrillation not "less than 3 months".

Minerva

Readers may have been seriously confused when Minerva wrote in one of her items that "exclusive breastfeeding is the best way for HIV positive mothers to feed their babies" (*BMJ* 2007;335:216, 28 Jul). It depends, of course, on the circumstances. Current international consensus guidance

from the World Health Organization states that exclusive breastfeeding is recommended for HIV infected women for the first six months of life "unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time," in which case, avoidance of all breastfeeding is recommended (www.who.int/child-adolescent-health/New_Publications/NUTRITION/consensus_statement.pdf).

Management of asthma in children

In this Clinical Review by J Townshend and colleagues (*BMJ* 2007;335:253-7, 4 Aug), a mix-up in terminology during editing was not picked up at proof stage, resulting in some confusion for readers. In the section headed "Long acting 2 agonists" five of the six references to "short acting 2 agonists" (all but in the final sentence) should have read "long acting 2 agonists." In addition, the second and third sentences in the Summary Points box should refer to "long acting 2 agonists not antagonists."

Diagnostic accuracy and clinical utility of a simplified low cost method of counting CD4 cells with flow cytometry in Malawi: diagnostic accuracy study

In this paper by Calman A MacLennan and colleagues, we gave the wrong unit for the CD4 cell count (*BMJ* 2007;335:190-4, 28 Jul). Throughout the article we gave the unit as $\times 10^9/l$, whereas the correct unit is cells/ μl (cells per microlitre). This error has been corrected in the online pdf and html versions of the article.