Regulating medicines in Europe: the European Medicines Agency, marketing authorisation, transparency and pharmacovigilance

Govin Permanand, Elias Mossialos and Martin McKee

ABSTRACT – Following a review process lasting almost four years, and culminating in several pieces of new European legislation, adjustments have been made to the European Union's (EU) regulatory framework for pharmaceuticals. The European Commission laid out its priorities for the review as: simplifying the authorisation system, ensuring a high quality of public health, completing the internal market in medicines, and preparing for the enlargement of the Union. Amongst the most important changes brought about by the new rules are those relating to the European drug approval procedures, the functions and operational transparency of the European Medicines Agency (EMEA), and the EU's pharmacovigilance system. This article provides a brief examination of key elements of these changes, and considers the extent to which they serve the goal of improved public health protection within the EU.

KEY WORDS: drug approval procedures, European Medicines Agency, European Union, pharmacovigilance, review of pharmaceutical legislation, transparency

The European Community first took action on pharmaceuticals in 1965, in the aftermath of the Thalidomide tragedy, to establish certain basic safety procedures. During the 1970s and 1980s, closer economic ties between countries made it necessary to act in a number of areas, with the momentum created by the single European Market, established in 1992, bringing a raft of measures for the harmonisation of drug approval. In 1995, the system was institutionalised with the creation of the European Agency for the Evaluation of Medicinal Products, now the European Medicines Agency (EMEA). This was to complement national procedures by offering a centralised pan-European approval regime. From the outset the EMEA has been dogged by criticism, focusing on the balance between speed and quality, and independence and transparency in drug approvals.[1,2] Following a recent review of European Union (EU) rules on pharmaceutical regulation, the EMEA is, however, changing.[3] This paper provides an up-to-date review of these new developments, focusing on the EMEA's market authorisation procedures, transparency and pharmacovigilance systems, asking how well they serve the citizens of Europe.

Marketing authorisation procedures

The creation of the EMEA established two new procedures for the approval of drugs. First, biotechnology and other high technology products must undergo a centralised approval process; this is optional for other products. One national agency undertakes the scientific evaluation, and the assessment process is overseen by the agency's Committee for Proprietary Medicinal Products, now the Committee on Human Medicinal Products (CHMP). A second, decentralised, procedure is undertaken at national level. Applications go to the 'Reference Member State', the market in which the company wishes to first launch its product, and the agency facilitates recognition of marketing authorisation by other 'Concerned Member States'. The pre-existing national procedure remains for applicants targeting only single countries. Although the core elements in these procedures have not been changed under the new rules, there have been some adjustments.

The centralised procedure has been extended to cover orphan drugs (intended to treat serious conditions affecting fewer than 5 in 10,000 persons), and products containing a new active substance not previously authorised within the EU and which are for the treatment of HIV/AIDS, cancer, diabetes or neurodegenerative disorders. After 4 years this list will be extended to medicines for the treatment of autoimmune and other immunological diseases, and antiretrovirals. The procedure has been made optional for products constituting a 'significant innovation', although the EMEA has not developed criteria for what constitutes an innovation, instead depending on the 'opinion of the agency'. The EMEA is not charged with comparing the clinical efficacy of similar drugs. Unsurprisingly, therefore, the majority

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of centrally approved drugs have been 'me-toos',[4] limiting the scope for national officials to reject approvals on the grounds of cost-effectiveness.

There is an attempt to speed things up. A 210-day review period for both centralised and decentralised procedures remains, but where an applicant drug is 'of major interest from the point of view of public health and in particular from the point of view of therapeutic innovation', the turnover time is reduced to 150 days. However, in the absence of a clear definition of innovation (taking comparative clinical efficiency into account), this provision may be misused. Subject to 'justified public health reasons', the rules also permit member states to force a product onto the market that has not yet received marketing authorisation, eg when faced with bioterrorism or an acute outbreak of a rapidly spreading illness. However, these decisions remain the prerogative of each member state.

Conditional marketing authorisations are now also permitted. These are to be granted on a yearly basis and revised annually. The Commission proposes that these should apply to drugs 'aimed at the treatment, prevention or medical diagnosis of chronically or seriously debilitating diseases or life-threatening diseases' and orphan drugs, and for use in emergency situations in response to public health threats. There is concern about the breadth of these provisions. The European Organisation for Rare Diseases has questioned whether these provisions actually serve 'the public health interest'[5] and, notwithstanding the lack of criteria for what is innovation, it seems particularly worrying that there is no requirement for any sort of comparative clinical assessment. At the request of the Commission, the EMEA will, however, 'collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal products provide'. This is the first time that any reference to comparative efficacy has featured in EU medicines legislation, but what it will mean in practice is unclear.

A 'compassionate use' clause has also been added. Provided clinical trials are underway and an application has been filed, drugs under review via the centralised procedure can be granted a provisional licence if they are for patients 'with a chronically or seriously debilitating disease or whose disease is considered to be life threatening, and who cannot be treated satisfactorily by an authorised medicinal product'. A similar scheme exists in France where such drugs are even covered by social insurance. This will have to be closely monitored as it may lead to drugs being authorised on the basis of early trial data, but which are subsequently shown to be less valuable than thought – as with the 2003 approval of Iressa® in the USA for the treatment of small cell lung cancer in cases where other therapy had failed. Here, on the basis of early results showing tumour shrinkage, it was assumed that trials then in progress would show that this was associated with prolonged survival but, when they eventually did report, the drug was found to confer no significant survival advantage. Vigilance will, therefore, be crucial.

Authorisations are to be subject to a mandatory 5-year reassessment. As no further review will be required, it is important that this reassessment is rigorous. The protocol should, at a minimum, include a review of the original evidence, as well as covering quality testing, compliance with manufacturing standards, pharmacovigilance, and inspections of manufacturing facilities. As new indications may have been found since the initial authorisation, or newer products with fewer side effects may have become available, these considerations too ought to be taken into account. However, it is not clear that the EMEA has the resources to do this. The EMEA (and national authorities) might, therefore, be advised to consider drawing on the expertise and experience of external bodies to collate evidence and provide independent systematic reviews, eg the Cochrane Collaboration.

The agency's management board will now include two representatives from patient organisations and one from doctors' groups as nominated by the Commission. While the formal inclusion of patients' interests is a positive development, the larger patient and consumer groups are often financed by the pharmaceutical industry,[6] as is the case with the European Patients' Forum, which is now represented on the board.[7]

Transparency

The EMEA has long been criticised for insufficient transparency.[8–10] The new rules introduce several provisions to tackle this. National authorities must now make their rules of procedure publicly accessible, with details of meetings and minutes. After granting approval, authorities will now be required to make available 'without delay' the marketing authorisation, the Summary of Product Characteristics (submitted with an application and outlining the scientific data and clinical effectiveness details for the product), the assessment report, and reasons for the opinion (commercially sensitive data will be deleted). Previously, national agencies were not bound to make public the results of their evaluations.

The majority of EMEA documentation will now fall under existing EU legislation governing public access to documents held by other European institutions. The agency already makes information available on its website, but it must now produce a public register of all its documents, including internal rules and procedures. Opinions will be published and any refusals under the centralised procedure are to be made publicly accessible; previously only the results of positive applications were released. Under the decentralised procedure, applicants will no longer be permitted to withdraw an application. Information on serious adverse drug reactions (ADRs) and other pharmacovigilance data will now be publicly accessible 'if relevant' and 'after evaluation', although these caveats do not suggest a commitment to increased transparency.

European Public Assessment Reports (EPARs), which provide assessments of new applications granted a positive opinion by the EMEA, have also been addressed in the new rules. Although less than some critics would have liked,[11,12] their content must now be written 'in a manner that is understandable to the public', and must include an explicit summary of the product's conditions of use. Nevertheless, this does not address the findings of a recent review of those reports available via the EMEA website, where 'contradictory conclusions on the effect of the

drug on HRQOL [Health-related Quality of Life] are presented in different EPARs for the same substance.'[13]

Centralised approvals will now require the inclusion of the International Nonproprietary Name in the application and on the leaflet and packaging. This will help health professionals and patients to identify which drugs or indications are actually new. The readability of the leaflets is to be improved, as companies will be required to cooperate with patient groups in drafting them before submitting the application. Fines levied against companies for noncompliance are to be published, with amounts and reasons. Where a company seeks to withdraw an application before an opinion has been given, it must now set out its reasoning to the EMEA.

While these efforts will go some way to addressing the concerns expressed by numerous commentators about the secrecy surrounding not just decision-making but the EMEA authorisations themselves,[1,4] there is still a long way to go. The US Food and Drug Administration (FDA) has traditionally been more open and accessible, and not only is its website easier to navigate than the EMEA's, but the information it carries is targeted at specific user groups, ie the elderly, physicians, consumers or healthcare professionals. Information on evaluations is posted and the FDA discloses research information on preclinical and clinical trials. Approvals are accompanied by explanations of the justifications, and the information submitted by the applicant is summarised on the website; anyone is entitled to request access to this information. Notwithstanding recent accusations that the FDA may have suppressed information about several drugs, notably Vioxx®,[14] the EMEA's new transparency provisions are playing catch-up.

Pharmacovigilance

Despite several pieces of EU legislation relating to post-market surveillance of medicines[15] – including that which established the agency – the Community's pharmacovigilance system needs strengthening. ADR reporting in Europe is generally low,[16] and although improving in terms of frequency of reporting,[17] there are still concerns about quality, which the new rules fail to address. Suggestions from interest groups that patients be encouraged to report any adverse reactions directly to their competent authorities were not taken up.[18] And while the Summaries of Product Characteristics ought to include information on ADRs (eg type and frequency of events), this too does not feature in the new legislation. Nor are the summaries themselves required to contain references to comparable products already available on the market; this would clearly help healthcare professionals in their prescribing choices. However, comparative therapeutic benefit does not feature anywhere in the agency's work.

Nevertheless, the new legislation does address the Community's electronic tracking and reporting system for safety reports, EudraVigilance (www.eudravigilance.org). The aim is to implement a reporting system based on standardised pharmacological data and to develop a common EU reporting procedure. This will involve the (electronic) exchange of national data, evaluation, quality control and risk monitoring information between the EMEA, competent authorities and companies holding marketing authorisations. The EudraVigilance system will now include preapproval safety data (postapproval data are already covered), and a higher degree of openness and public access is envisaged. By comparison, and notwithstanding the apparent failure in relation to Vioxx®, the FDA's pharmacovigilance competences have traditionally been stronger. What the Vioxx® example highlights for both agencies, however, is the need for high quality monitoring systems.

The EMEA is thus to establish and manage a publicly accessible database containing pharmacovigilance information collected by the member states. This is laudable, but neither the operational aspects of the database nor how it will be established ('in stages') has been developed. There are also questions as to who will run it and how often it will be updated. One detailed study has already shown that there is a dearth of professional statisticians working for drug regulatory authorities in Europe, and a critical need for statisticians and biostatisticians at the EMEA.[19] The new proposals make no commitments here. Nor have the details on funding been outlined, although there is an explicit stipulation that industry will not be involved.

More clarity is offered regarding pharmacovigilance requirements in marketing authorisation applications themselves. Along with a 'detailed description of the pharmacovigilance', applications now need to be accompanied by evidence of the services of a qualified person, and the applicant must demonstrate the necessary means for notification of ADRs. Inspections are to be made routine, a system for the recognition of inspections is to be introduced, and authorisation holders will be required to submit Periodic Safety Update Reviews (PSURs) on a more regular basis than previously. Each review must also make clear what new information has been added – this will be especially useful in regard to combination substances that are otherwise individually registered – and the PSURs are to be cross-referenced. Within the context of assessing product safety and the risk-benefit profile more generally, companies will be obliged to provide data on sales and prescription volumes upon request by a national agency.

Finally, although all funding for pharmacovigilance purposes is to be independent of industry, this is not the same as saying that all pharmacovigilance funds must come from public sources.

Final remarks

The Commission's new rules have effected several changes in relation to the EMEA *vis-à-vis* market authorisation procedures, transparency and pharmacovigilance. Public health interests appear to have been given a higher priority than in the past, where the results did not match the rhetoric. Specifically, the enabling of approvals on 'compassionate use' grounds, the inclusion of patients' and doctors' representatives on the EMEA management board, increased transparency requirements and an improved commitment to post-marketing surveillance of drugs are valuable additions. However, several problems and

gaps remain, and putting many of the proposals into practice is likely to prove a challenge.

Amongst the most glaring gaps in the agency's remit is the continued lack of an EU-level provision for comparative clinical efficacy; whether as an official criterion in the review process or as part of an application submission. Drugs continue to be assessed in isolation and the scientific information pertaining to them makes no reference to comparator products. Additionally, the agency continues to suffer in relation to capacity issues. There appear to be insufficient personnel, expertise and independent financing to fulfil many of its new commitments. Questions relating to the operation of the new pharmacovigilance database – not to mention the new clinical trials and paediatric information databases proposed under separate legislation – have yet to be addressed.

Finally, despite 20 November 2005 having been the official implementation date, concerns are likely to remain over the member states' and national regulatory authorities' commitment. For not only is the transposition of EU rules into national law often sketchy, but with regard to national medicines and healthcare policy, it is especially sensitive. So while, for all their failings, the new changes do promise much, the extent to which the proposals will be able to deliver is not yet clear.

References

1 Abraham J, Lewis G. *Regulating medicines in Europe: Competition, expertise and public health*. London: Routledge, 2000.

2 Garattini S, Bertele' V. The role of the EMEA in regulating pharmaceutical products. In Mossialos E, Mrazek M, Walley T (eds), *Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality*. European Observatory on Health Systems and Policies Series. Maidenhead: Open University Press, 2004.

3 Commission of the European Communities. Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Directive 2004/28/EC amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products. Directive 2004/24/EC amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official J Eur Communities* L131 2004;30 Apr:1–90.

4 Garattini S, Bertele' V. Adjusting Europe's drug regulation to public health needs. *Lancet* 2001;**358**:64–7.

5 European Organisation for Rare Diseases. *Eurordis comments on the draft regulation on conditional marketing authorisation for pharmaceutical products – submission to the European Commission*. Paris: European Organisation for Rare Diseases, 2005.

6 Herxheimer A. Relationships between the pharmaceutical industry and patients' organisations. *BMJ* 2003;**326**:1208–10.

7 Health Action International. *Does the European Patients' Forum represent patient or industry interests? A case-study in the need for financial disclosure*. Amsterdam: Health Action International, 2005.

8 Abbasi K, Herxheimer A. The European Medicines Evaluation Agency: open to criticism. Transparency must be coupled with greater rigour. *BMJ* 1998;**317**:898–900.

9 International Society of Drug Bulletins. *The failings of the EMEA*. ISDB Position Paper. Paris: International Society of Drug Bulletins, 2000.

10 Medicines in Europe Forum. European pharmaceutical policy is turning its back on public health. *Prescrire Int* 2002;**22**:464–6.

11 International Society of Drug Bulletins. *ISDB assessment of nine European Public Assessment Reports published by the European Medicines Evaluation Agency between September 1996 and August 1997*. Paris: International Society of Drug Bulletins, 1998.

12 Anonymous. European Medicines Evaluation Agency (editorial). *Int Soc Drug Bull Newsletters* 2001;**15**:11–3.

13 Papanicolaou S, Sykes D, Mossialos E. EMEA and the evaluation of health-related quality of life data in the drug regulatory process. *Int J Health Tech Assess* 2004;**20**:311-24.

14 Kaufman M. FDA official alleges pressure to suppress Vioxx findings. *Washington Post* 8 Oct 2004: A23.

15 Commission of the European Communities. Commission Regulation (EC) No 540/95 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use. *Official J Eur Communities* L55 2003;11 March:5–6.

16 Heeley E, Riley J, Layton D, Wilton LV, Shakir SAW. Prescription-event monitoring and reporting adverse drug reactions. *Lancet* 2001;**358**: 1872–3.

17 Fleuranceu-Morel P. How do pharmaceutical companies handle consumer adverse drug reaction reports? An overview based on a survey of French drug safety managers and officers. *Pharmacoepidemiol Drug Safety* 2002;**11**:37–44.

18 Medicines in Europe Forum. Medicines in Europe: citizens' successes. *Prescrire Int* 2004;**24**:542–8.

19 Köpcke W, Jones DR, Huitfeldt B, Schmidt K. Statistics and statisticians in European Drug Regulatory Agencies. *Drug Information J* 1998;**32**: 243–51.