REGULATORY NEWS

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Marketing authorisations and public health: the European Commission's minimalist guidelines

In order to ensure the minimum effectiveness and safety of new medicines, drug companies must obtain authorisation before marketing their products in Europe.

There are three marketing authorisation procedures in Europe: the centralised procedure, the national procedure, and the mutual recognition procedure.

In the centralised procedure, authorisation is granted by the European Commission's Enterprise and Industry Directorate-General, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. Authorisations granted in this manner are binding on all Member States. In the national procedure, marketing authorisation is granted by the regulatory agency of an individual Member State, and is only legally binding in the country concerned. Finally, in the mutual recognition procedure, Member States individually endorse a marketing authorisation that has already been granted by another Member State.

Greatly appreciated by drug companies for its "flexibility", the mutual recognition procedure has come in for sharp criticism since the 1990s. Various organisations, including the Medicines in Europe Forum (1,2), have condemned its opacity and the unhealthy competition it creates among national regulatory agencies (**a**)(2).

Directive 2004/27/EC and Regulation 726/2004 on human medicines broadened the scope of the centralised procedure but did not abolish the mutual recognition procedure (3,4). However, the rules governing mutual recognition were strengthened, and, if the new provisions are properly transposed in all Member States, the procedure should become more transparent.

Article 29 of the 2004 Directive specifies what happens when, during the mutual recognition procedure, one Member State refuses to endorse the assessment report of another Member State's regulatory agency, or the proposed summary of product characteristics (SPC) or patient information leaflet, because of a "*potential serious risk to public health*" (3). Article 29 also states that "*Guidelines to be adopted by the Commission* (Enterprise and Industry Directorate-General) *shall define a potential serious risk to public health*" (4).

The Commission's chief concern: free movement of goods. In February 2005 the European Commission published its guidelines defining "a potential serious risk for public health", applicable as of November 2005 (5). The front cover of the document specifies that the only contributors were the 3 main pharmaceutical industry associations in Europe: the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Generics Association (EGA), and the Association of the European Self-Medication Industry (AESGP).

The introduction emphasises that a Member State which disagrees with another Member State's recommendation to grant marketing authorisation must provide a detailed and substantiated justification for its objections, based on a potential serious risk. The rationale for these provisions is to avoid hindering "*the free movement of goods*". "*A serious risk in this context means a hazard that could result in death, could be life-threatening, could result in significant disability or incapacity, could be a congenital anomaly/birth defect, or which could result in hospitalisation or permanent or prolonged signs in exposed humans*". This definition covers most of the potential negative consequences of using a drug and, in theory, provides Member States with the means to raise objections whenever necessary.

In practice, however, the Commission's interpretation of this definition is somewhat surprising, to say the least.

A minimal assessment is considered sufficient to protect patients. The annex to these guidelines lists examples of conditions or situations that should not be considered grounds for a serious risk to public health. According to the European Commission, the following situations do not represent a danger to the public:

– The absence of an active comparator study versus a specific medicinal product;

– The absence of evidence demonstrating added therapeutic value of the new medicine in comparison to existing medicines;

– The length of the treatment varies according to national medical practices in the various Member States;

– The targeted population is too narrow, and should include patients who are allergic or intolerant to medicinal products approved for the same indications;

– For products with well-established medicinal use the posology is based on systematic and documented use and the safety is based on pharmacovigilance data;

– The absence of contra-indications from other medicinal products of the same class, if the scientific data provided in the documentation gives no reason to believe that the same contra-indications apply to the new medicine.

Patients exposed to drugs with no proven therapeutic advantage. Thus, according to the Enterprise and Industry Directorate-General of the European Commission, major gaps in a drug's clinical assessment do not represent a danger for patients.

In practice, Member States are expected to accept, without raising objections, drugs assessed only in placebo-controlled trials, in adults with no particular risk factors, drugs whose benefits compared to existing drugs of the same class and optimal dose regimens are unknown, and drugs for which the duration of treatment differs from that usually prescribed.

In light of recent drug scandals, some of which resulted from inadequate initial assessment, these guidelines can easily be seen to represent a danger to public health (6), placing patients at risk from new drugs with no proven therapeutic advantage.

Time to react. Drugs are not simple consumer goods that can be sold without restriction. If the European Commission's guidelines fail to take patients' safety into account, Member States are duty-bound to challenge them (**b**).

European citizens must lobby European institutions and their national governments to ensure that, at the very least, in the field of healthcare products EU citizens' interests are placed ahead of the "free movement of goods".

a- Regulatory agencies are mainly financed through the licensing fees that companies pay to have their marketing applications examined, and for advice on preparing their application files.

b- When a Member State refuses to endorse a marketing authorisation because of a potential risk, Directive 2004 calls for arbitration by the European Medicines Agency CHMP. However, other Member States deciding to endorse the marketing authorisation can allow the drug to be marketed in their country without waiting for the end of the arbitration procedure (article 29-6 of the Directive) (ref 3).

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "En pratique, la politique du médicament tourne le dos à la santé publique" *Rev Prescrire* 2002; **22** (229): 464-466.

2- Prescrire Rédaction "Les dangers de la procédure d'AMM par reconnaissance mutuelle" *Rev Prescrire* 2002; **22** (230): 542.

3- "Directive 2004/27/EC of the European parliament and of the council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use" *Official Journal of the European Union* 30 April 2004: L136/34 - L 136/57.

4- "Regulation (EC) no 726/2004 of the European parliament and of the council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency" *Official Journal of the European Union* 30 April 2004: L 136/1 - L 136/33.

5- European Commission - Enterprise and Industry Directorate-General - Consumer goods - Pharmaceuticals "Proposal for a Guideline on the definition of a potential serious risk to public health" February 2005: 5 pages.

6- Prescrire Editorial Staff "How to avoid future Vioxx°-type scandals" *Prescrire Int* 2005; **14** (77): 115-117.

ABOUT PRESCRIRE

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News of Prescrire network

Sales first

Year after year, members of Prescrire Sales Representative Monitoring Network have reported the same breaches of regulatory requirements for accuracy, completeness and consistency with approved product labelling in the claims made by drug company salespeople, including: a tendency to promote off-licence uses and to understate potential risks, and a general failure to provide legally required documents.

These breaches are hardly surprising when one compares the legal framework that is supposed to improve the quality of sales representatives' visits with what goes on in the field.

The introduction to the French sales representatives' charter, which came into effect in 2004, states that (our translation): "*in accordance with the law, the Charter (…) aims to strengthen the role of sales representatives in promoting rational use of medicines and high-quality information.*"

Meanwhile, the programme of the annual Sales Forces Effectiveness Europe conference, held this year from 13 to 15 March 2006 in Barcelona, reveals a totally different image of sales representatives. Take these extracts from the programme, for instance:

– "Expert tips on how to use your training plans as motivational tools for your sales force";
– "How Eli Lilly increased productivity with optimal sales force deployment and sizing";
– "Find out how Novartis built a Selling Effectiveness culture that delivered dramatic results";
– "Learn how to provide GPs with value added services to maximise your customer access and increase sales".

The entire programme, and the list of sponsors (Cegedim, Ims, etc.), can be obtained from http://www.SFEeurope.com

The Prescrire Sales Reps Monitoring Network

Coming soon. The next issue will carry a comprehensive review of 15 years of Prescrire Sales Representative Monitoring Network.