REGULATORY NEWS

EMEA drafts for public consultation

Make your voice heard

For several years the European Medicines Evaluation Agency has regularly submitted to public consultation online some of its draft texts, recommendations and proposals on the assessment of marketing applications and the general functioning of the agency. The consultation period generally lasts a few months.
All European citizens and professional groups can send comments, in any of the official EU languages. And it is simple: visit the What's new/Recent publications page on the EMEA website (http://www.emea.eu.int/whatsnewp.htm), access the documents (listed in chronological order) and download the texts offered for public comment. The only constraint is a deadline for comments. The texts should be considered in context, most being continuations, revisions or modifications of previous texts. The introduction should therefore be read carefully, as it will mention previous texts and their legislative framework, distinguishing EMEA documents and guidelines (which are not binding) from Directives and Regulations.
For example, on 24 February 2004 EMEA placed online a document entitled "Guideline on the format and content of applications for designation as orphan medicinal products and the transfer of designations from one sponsor to another" (http://www.emea.eu.int/pdfs/human/comp/628300en.pdf).
And on 22 April 2004 it released a document dealing with patient information, entitled "EMEA/CPMP Working Group with Patients Organisations - Outcome of Discussions: Recommendations and Proposals for Action (http://www.emea.eu.int/pdfs/human/patientgroup/581904.pdf)
The Prescrire editorial staff contributed the following comments.

Ambiguities in orphan drug designation in the EU

Patients' interest is not sufficiently safeguarded

"We have carefully read the draft revision, dated 24 February 2004, of the guideline entitled: "Guideline on the format and content of applications for designation as orphan medicinal products and the transfer of designations from one sponsor to another". This document concerns an important area of public health, namely rare but often life-threatening diseases. We are pleased to see that European Commission is dealing with this question and is trying to strike a balance between health requirements and the interests of drug manufacturers.

Significant benefit. This document clarifies the general principles outlined in Regulations 141/2000 and 847/2000. Regulation 141/2000 states that the notion of "significant benefit" relative to existing treatments must be taken into account before a new drug can be designated an "orphan drug". The definition of "significant benefit" (pages 11-12 of the document, paragraph 3 of the new guideline) is precise, and rightly insists on demonstrable clinical benefit, in terms of efficacy or adverse effects, relative to existing treatments.

The value of this definition is, however, negated by the end of this section, which states that wider distribution of a new drug relative to existing treatments itself represents "significant benefit". This principle, which links " benefit" to market availability, was not contained in Regulations 141/2000 and 847/2000. It appeared in successive drafts of the guideline now undergoing revision, but it is incompatible with patients' and health professionals' expectations. If a drug offers no advance in terms of the risk-benefit balance or convenience, it should not be granted orphan drug status simply because it is more readily available than an existing treatment. The Commission's role should be to help ensure that existing reference treatments are available in all EU member states, without waiting for a company to exploit the situation.

Ambiguities. Page 7, paragraph c of the section on "Special Considerations" is rather vague, and opens the door to multiple interpretations. The expression "particular treatment modality" is imprecise, and we fail to see how it can define a "distinct condition". The term "treatment modality" must be defined unambiguously in the text.

Furthermore, this text, and Regulations 141/2000 and 847/2000, say nothing about the lifespan of orphan drug status.

European law, including the new regulation published on 30 April 2004, calls for reassessment of marketing authorisation once a drug has been on the market for five years, and this also applies to orphan drugs. This should be an opportunity to examine whether "orphan drug" status is still justified. In particular, pharmacoepidemiological data should be examined to check that the orphan drug is being used as intended, and that the number of patients treated corresponds to the definition of an orphan disease (maximal prevalence 5 per 10 000 inhabitants).

This may be the case in practice, but it is a key point that should be explicitly mentioned in the new guideline".

Problems in the EMEA patient information working group

Too drug oriented, too many conflicts of interest

"We have read in detail the document EMEA/CPMP/5819/04/Final dealing with patient information, entitled "EMEA/CPMP Working Group with Patients Organisations - Outcome of Discussions: Recommendations and Proposals for Action".

La revue Prescrire has been assessing the quality of patient information for more than 20 years, on behalf of its subscribing doctors and pharmacists. We have therefore followed with interest the activity of the "Working group with Patients organisations" since its creation a few years ago.

We would like to draw the attention of the working group members and the EMEA to a number of methodological problems that undermine the validity of the recommendations offered for public consultation.

Applying the Regulation. We regret that the Working Group's recommendations do not sufficiently take into account the new Regulation 726/2004 that defines the framework of EMEA activities and its implementation schedule. We note that title IV applies immediately, and that EMEA now has an obligation of transparency, in application of European Regulation 1049/2001 on public access to documents, and in keeping with the spirit of the Charter of Fundamental Rights of the European Union. According to article 73 of Regulation 726/2004, the EMEA management board must ensure that these obligations are implemented within 6 months of the publication of Regulation 726/2004 in the Official Journal (i.e. on 30 October 2004).

Conflicts of interest. We also note that many patient organisations participating in the working group receive various degrees of financial support from drug companies. According to its website, the patient group IAPO, for example (see List of Participants), is funded by drug companies. The fact that an IAPO member is rapporteur for the document entitled *Recommendations in the area of transparency and dissemination of information* (Annex 2) creates a serious conflict of interest.

Public confidence, not to mention the credibility of EMEA's scientific work, demands that all conflicts of interest be clearly listed. Regulation 726/2004 (article 63.2) defines EMEA's obligations regarding conflicts of interest. These obligations also apply to working group members. EMEA must therefore ask members of the Working Group with Patients Organisations to declare their conflicts of interest, and must make them readily accessible on the EMEA website. To our knowledge, this is not the case.

Package leaflets. Before proposing improvements to package leaflets, we think patient groups should first evaluate their defects and inadequacies, in total independence from drug companies, and in collaboration with health professionals (prescribers, pharmacists and nurses), who, it should be said, are inadequately represented in the working group. To our knowledge, this is not the case.

Currently, package leaflets are full of administrative jargon, their contents appear in no prioritised order, and they are poorly suited to the situations that patients most often encounter. Basically, they serve simply to protect manufacturers and medicines agencies from legal action.

Contrary to what is being recommended, it is in no way desirable to stress a drug's expected benefits to the detriment of its risks. What patients need is balanced, comparative information. As a rule package leaflets contain no data from comparisons with other treatments. Stressing the expected benefits would therefore be equivalent to surreptitious advertising, and would divert patients' attention away from possible adverse effects.

The inadequacies of EPARs. The consultative document asserts that EPARs have benefited health professionals and recommends that EMEA might produce "*a patient friendly version reflecting any comparisons with existing therapeutic options*". The quality and interest of EPARs were assessed by an ISDB member group on two occasions, in 1998 and 2001 (1,2). Their conclusions were highly critical, and the situation has barely improved since:

– the clinical assessment section is far from systematically complete and detailed;
– the adverse drug reaction section varies widely in quality from one EPAR to another;
– virtually no information is given on CPMP experts' questions or misgivings;
– dissenting or minority voices within the CPMP are not mentioned;
– there are no data from comparative assessments and no information on added therapeutic value relative to existing treatments, which is of course in line with the law, but does not permit a "reflection" of useful comparisons".

Proposals of the Prescrire Editorial Staff

- The patient information on diseases and treatments that EMEA is planning to publish online should include the existing drug and non-drug treatments, as well as preventive measures. The public must not be given the impression that medicines are the only answer to all health problems. The information should also include comparative data on existing treatments (added therapeutic value).
- EMEA should provide European citizens with basic information, in the style of "frequently asked questions", on epidemiology, clinical trial methodology, risk-benefit balance, natural outcome of diseases, placebo effect, and pharmacovigilance. Without a minimum of signposts, patients and the public are easily misled by the plethora of pseudoscientific information that they cannot understand. In these conditions, "communication" is simply a smoke-screen.
- The EMEA search engine should allow drug information searches based on international non proprietary names (INN).
- The information contained in package leaflets should be given in the order of importance of expected benefits and possible dangers, and should clearly distinguish established fact from assumptions. The objective is to optimise compliance without minimising adverse effects.
- The information should be presented as simple questions and answers, accompanied if necessary by pictograms.
- A major place should be set aside for health advice and health education, in order to improve rational use of drugs.

1- "ISDB assessment of nine European public assessment reports published by the European Medicines Evaluation Agency" International Society of Drug Bulletins, 1998.
2- "The failings of the European Medicines Evaluation Agency" *ISDB Newsletter* 2001; **15** (1): 11-13.