

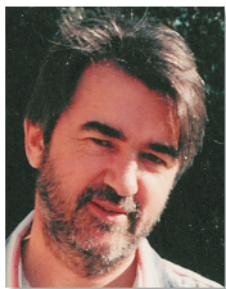
Some Do—Some Watch Over Those Who Do

Peter O'Donnell

Europe's regulatory authorities try to remain one step ahead of the pharmaceutical industry, which in turn watches the watchers in Europe's evolving regulatory environment.

Europe derives much of its strength as a center for clinical trials from the excellence of its investigators, the continuing vigor of the pharmaceutical industry operating there, and the generally high esteem in which European medical science is held.

But those who do—who are professionally involved in clinical trials—are not the only factors in the equation. Part of the European evolution toward greater international respectability and influence in clinical trials depends on what happens among those who watch over them.



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And a major component among those who watch is the European Agency for the Evaluation of Medicinal Products (EMA) in London. As reported in this column in May, big changes will be proposed shortly to the European Union legislation that governs the way the EMA works (more on this theme below). But smaller changes are being made all the time to the way the EMA operates—designed to make it more efficient, and to make it more useful to the pharmaceutical companies that discover and develop drugs.

One of the latest examples of this small-scale evolution is the recent appearance of what is entitled a “presubmission meeting request form” from the EMA. It is more than another piece of Brussels bureaucracy. It should, in fact, add another piece to the gradually evolving mosaic of a success-oriented EU regulatory system.

The presubmission meeting request form

The EMA has for several years now offered the chance for applicants—or potential applicants—to discuss their products, informally and formally, with experts before they finalize and send in their applications for marketing authorization. The facility exists to ease the passage of new drugs from concept to commercialization—by clarifying gray areas before product development plans are crystallized. This focuses protocols more exactly on what the EU regulators want to see in support of an application, and helps to avoid the exploration of blind alleys that will be expensive in financial and management terms.

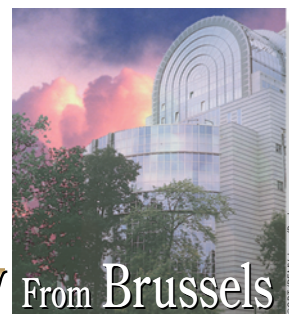
One of the possibilities within this system is that companies developing new products that are to be assessed via the EU's centralized procedure can request a presubmission meeting with EMA experts. The new form is intended to

make this process more efficient and precise. These presubmission meetings are often concerned with strictly administrative questions—but questions that have nevertheless frequently held up and even frustrated drug applications in the past.

On the new form, companies may request clarification of specified topics by precisely phrasing their question and supplying relevant background information. The form requires the usual sort of administrative details about the applicant, the contact person, and the medicinal product in question—with details of trade name, active substance(s)/INN (international nonproprietary name), proposed ATC (anatomical, therapeutic, chemical) code, strengths, pharmaceutical forms, packaging and pack sizes, and proposed indications and posology. It asks for proposed dates for the meeting, the proposed date for submitting the application, a draft summary of product characteristics and labeling text, and other relevant draft documentation. Applicants are also asked to specify their justification for planning to submit the application through the centralized procedure (which is limited to biotechnology-derived products, new chemical entities, and other innovative products).

Then they are asked to indicate which of the standard areas for discussion they wish to raise at the meeting. If applicants wish to know if the proposed trade name is acceptable from a public health point of view, or what legal status could apply to it (that is, subject to medical prescription or not), they must indicate in advance that they wish to discuss this at the presubmission meeting. Similarly, they must say whether they wish to know when and how the key experts assessing their application (the “rapporteur” and “co-rapporteur” in EU parlance) will be

View From Brussels



appointed, whether they believe their product is eligible for accelerated assessment, and whether they will be submitting multiple applications for the same medicinal product. They may ask what fees they will have to pay, when package and product mock-ups and/or specimens must be submitted, and whether samples will have to be submitted together with the application.

This is also the time to clarify whether an application is supported by a European drug master file and whether the medicinal product contains or consists of genetically modified organisms, or contains (or uses in the manufacturing process) materials of animal and/or human origin. The latter is in light of the risk of transmissible spongiform encephalopathies. The

proposals for the bigger changes in prospect for the EU's drug authorization system. And in the weeks leading up to this commission decision (which itself will signal the start of a lengthy legislative and consultative process lasting probably more than a year), the European drug industry has been focusing on the issues that concern it most at this stage of the debate.

At the heart of industry worries are the rumored changes to the scope of the authorization system. The Commission has been quietly indicating that it may modify the current system so that companies developing new chemical entities (NCEs) will be obliged to use the centralized procedure—instead of merely having an option to use it, as at present. The European Federation of

procedure could also be relaxed, argues the industry.

Some biotechnology products will, the industry concedes, have to be dealt with through the centralized procedure, which is where sufficient regulatory expertise on the most advanced high-technology products can be mustered from across Europe. EFPIA urges that the classification used in the new Clinical Trials Directive could be used here, too—which would mean making the centralized procedure the obligatory route for those products for which prior approval is required for clinical trials. Those are gene therapy products, somatic cell therapy (including xenogeneic cell therapy), products containing genetically modified organisms, and other products with special characteristics.

But nowadays, not all biotechnology products should have to go through the centralized procedure, EFPIA continues. For instance, monoclonal antibodies could now be assessed through the mutual recognition procedure, because sufficient expertise in this branch of biotechnology has now accumulated across the national regulatory authorities of Europe. The essence of the EFPIA proposal is that the restrictions should reflect the current state of science—and since science is moving onward fast, so should the regulations.

Speeding pharmacovigilance

Meanwhile, technology is playing another role in the handling of regulatory affairs—this time in reporting of adverse effects, or pharmacovigilance as it is known in Europe. Taking into account the new developments in the area of electronic data exchange, the EMEA has agreed with EU national authorities and the European pharmaceutical industry to streamline the current operations and regulatory procedures in pharmacovigilance and to increase their cooperation. A just-agreed report records progress to date and sets out a work program to be conducted during 2001 and beyond. New developments in electronic data exchange are something that the International Conference on Harmonisation, also, has pushed forward in discussions between Europe, the United States, and Japan.

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application must specify the species and tissue from which any such material is a derivative, the country of origin of the source animals for the material cited, details of any certification of suitability of the material, of its intended use, and of the countries where donation took place.

Matters that can be raised also include whether qualified persons have been identified within the EU for pharmacovigilance, batch release, recalls, and scientific service. And they include the basic questions of how and to whom the applicant should submit the application dossier—how many paper and electronic copies, and the names and addresses of the members of the EMEA's scientific committee (the Committee for Proprietary Medicinal Products). Other issues include when the application should be submitted, the likely timetable for it to be evaluated, and when preapproval inspections for good clinical practice and good manufacturing practice may be expected.

Preparing for bigger changes

By the time this issue of *Applied Clinical Trials* is on your desk, the European Commission should have agreed its

Pharmaceutical Industries and Associations (EFPIA) has been arguing firmly that there is no reason to change the option into an obligation. Many companies (such as Novartis) do use the centralized procedure for most of their new chemical entities—but certainly not all of them, say industry experts. Many companies (often smaller ones, but also including giants such as AstraZeneca) still prefer to use the alternative procedure—known as “mutual recognition”—to get their products onto the still-separate European markets. And they want to be able to continue to do so; a first launch in, say, the UK then provides the platform for winning “recognition” of that authorization in other EU member states—some of them, or all of them. The mutual recognition system is also more congenial to applications based on co-marketing deals.

EFPIA says optionality should be maintained—and even expanded. Not only should companies with NCEs be allowed to use the mutual recognition procedure if they wish, but the current obligation for all biotechnology-derived medicines to use the centralized

The regulators and the industry had been trying during 2000 to define the basis for testing and implementing the ICH standards in pharmacovigilance, covering terminology, the data elements, and the message specifications for electronic transmission of individual case safety reports in the EU. On the basis of the results of the joint pilot, the preliminary testing exercise is being extended to ensure implementation of the ICH standards by all parties, and thus allow for the start of the regular electronic submission of these reports.

As a result, electronic safety reporting will replace paper reporting of adverse drug reactions (ADRs), regardless of the authorization procedure followed for the medicinal product. The mandatory deadlines for the implementation of electronic safety reporting in pharmacovigilance are to be set during 2001 by agreement among all the parties. Declarations of intent to use electronic exchange of safety reports will be sought from pharmaceutical companies with a product authorized anywhere in the EU

and from each of the EU's national regulatory authorities. The declarations are intended to define reporting partnerships between regulatory authorities and pharmaceutical companies, and to define appropriate contact points.

An electronic gateway is to be set up for the electronic transfer of regulatory information, to permit companies to report to a common regulatory point across the European Union using secure communication. Companies will send case safety reports to the established mailboxes of national regulatory authorities and EMEA using existing electronic routes, and acknowledgment messages will be sent to the sender via the same route, so as to ensure compatibility of information and communication tools and security of communication.

On terminology, the description of medicines and active substances—and the coding of pharmaceutical forms—should put into effect the provisions of 1999 guidelines produced by the EMEA

on electronic exchange of pharmacovigilance information. Further work is to be put in hand to overcome difficulties that arise because of differing local terminology—as, for instance, in the case of company drug codes used in clinical trials.

So while drug companies and researchers develop their new products, the regulators are trying to remain one step ahead, to ensure the most efficient regulation in a manner that minimizes unnecessary delays. The principle is the same as that of a passenger train running at high speed: the coaches offer little resistance, and will run easily on their own momentum. The locomotive, however, having dragged the carriages up to that speed, has to then expend energy to keep up its own speed, since its mechanism offers much more resistance, and if it does not stay ahead of the carriages, it will slow them down. Within the EMEA, therefore, the engine drivers are trying to keep their machine up to speed and ahead of the pharmaceutical industry train. □