Voluntary Clinical Trials Registration Sought

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In the face of bad publicity and impending restrictions, trade groups representing pharmaceutical companies have proposed a voluntary plan for using a clinical trials registry as well as results databases by midyear.

The "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trials Registries and Databases," issued by the Pharmaceutical Research and Manufacturers of America (PhRMA), sister organizations in Europe and Japan, and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) covers all nonexploratory (non–phase I) clinical drug trials and has two major requirements:

1. Clinical trials registry listing. All trials initiated on or after July 1, 2005, must be included in a clinical trials registry. Trials that are now underway must be included by Sept. 13, 2005.

Each trial "should be given a unique identifier to ensure transparency of clinical trial results" that would permit tracking the trial results through multiple databases. The U.S. government's trial registry site (www.clinicaltrials.gov) was specifically promoted as an acceptable registry model.

2. Timely posting of results. Results for all trials completed after Jan. 6, 2005, must be posted in a timely manner, generally within 1 year after the drug is first approved and commercially available in any country, or, for trials completed after approval, within 1 year of trial completion. An exception is made if posting would compromise publication in a peer-reviewed journal.

The database should include results of all non–phase I trials "conducted on a drug that is approved for marketing and is commercially available in at least one country," according to the proposal. Furthermore, the data must be disclosed "on a free, publicly accessible, clinical trials database, regardless of outcome."

The deadlines for registration outlined in the proposal match the mandatory deadlines issued by the International Committee of Medical Journal Editors last September. The ICMJE will require clinical trials registration prior to publication of drug trial results in member journals (including the Journal of the American Medical Association and the New England Journal of Medicine).

This mandatory requirement was one of the reasons the pharmaceutical groups included a registry in their proposal, Maciej Gajewski, manager of health care systems issues at IFPMA, told this newspaper.

But more significantly, the trade organizations hope that a voluntary international registry and results database will preempt the efforts of individual governments to enact their own clinical trials legislation that would make it difficult for member companies to operate efficiently on a global scale, Mr. Gajewski said.

For example, legislation was introduced in both houses of the U.S. Congress last October to mandate both trial registration and data disclosure. Although the bills did not pass, proponents say that they intend to submit similar bills this year, even in the face of the new pharmaceutical industry proposal.

A significant difference in the congressional approach is the introduction of penalties for noncompliance of up to $10,000 per day. In addition, their proposed registry (which would build upon www.clinicaltrials.gov) would include trials of biological products and devices, as well as drugs.

The focus in the position paper and the ICMJE statement (and mirrored in the federal legislation) on using www.clinicaltrials.gov is controversial. Last year, editors at the British Medical Journal refused to fully join their ICMJE peers and rejected the premise that that registry was the only appropriate option.

In a September 2004 editorial, Kamran Abbasi, acting editor of the BMJ, called www.clinicaltrials.gov restrictive in its requirements that drug trials follow certain U.S. requirements, including the filing of an investigational new drug application at the Food and Drug Administration. His journal is concerned that many nondrug, non–NIH-sponsored trials from developing countries would be excluded. "These restrictive entry criteria will not be met by many trials worldwide," Mr. Abbasi wrote.

Requiring worldwide adherence to FDA regulations also concerns the IFPMA, Mr. Gajewski said, because "more and more trials are being conducted in developing countries."

Although the industry's current proposal does not address the posting of historical clinical trials data, individual member companies have previously gone beyond the requirements of the position paper and included historical reporting, said Mr. Gajewski, and he believes they are likely to do so in the future.

He declined to comment, however, on the next steps in moving forward with the clinical trials registration and the databases, given that some of these events involve nonpublic, industry-related issues.

Last October, PhRMA launched its own results database for use by health care professionals and the general public (www.clinicalstudyresults.org). The database provides a home for industrywide voluntary listing of nonhypothesis testing drug clinical trials completed since October 2002 for all approved drugs. ■

Big Pharma's Annus Horribilis

Not everything went wrong for big pharma last year, but it might have seemed that way to some companies. Attacks came on several fronts, from journal articles to journal editors to the courts, and even legislators in the U.S. Congress and British Parliament.

In May, a report in the Journal of the American Medical Association highlighted the need for full disclosure by the industry of drug trial outcomes. An-Wen Chan, M.D., and colleagues at the Centre for Statistics and Medicine, Oxford, England, reviewed the original reports behind 122 published studies of 102 clinical trials. They found that overall, 50% of efficacy outcomes and 65% of harm outcomes per trial were incompletely reported. Furthermore, 86% (42 of 49) of trial investigators surveyed denied the existence of unreported outcomes despite clear evidence to the contrary (JAMA 2004;291:2457-65).

"The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention," the study authors wrote.

In June, the American Medical Association endorsed the concept of clinical trial registration, and GlaxoSmithKline was sued by the state of New York for concealing negative information from clinical trials related to Paxil.

In August, GSK agreed to a settlement that required posting a summary on its corporate Web site of every company-sponsored drug trial completed after Dec. 27, 2000.

In September, Forest Laboratories, manufacturers of the antidepressants Lexapro (escitalopram) and Celexa (citalopram) in a separate agreement with the state of New York, said it would post clinical study results completed since Jan. 1, 2000, for its marketed drugs.

That same month, the International Committee of Medical Journal Editors (including the editors of the Journal of the American Medical Association, the New England Journal of Medicine, and the British Medical Journal) issued a requirement that clinical trials be registered by July 1, 2005, for results to be published in member journals.

Finally, problems with cyclooxygenase-2 (COX-2) drugs came to light, and Merck pulled Vioxx (rofecoxib) off the market after its own study revealed an association between the use of the drug and an increased the risk of cardiovascular events.

In October, bills were introduced (but not passed) in the U.S. Congress that would mandate registration of all clinical trials and provide penalties of up to $10,000 per day for noncompliance.

And in November 2004, the Medicines and Healthcare Products Regulatory Authority (the British version of the U.S. FDA) announced its intention to add members of the general public to its regulation of medicines committee, in part to limit industry influence. The head of the agency wrote to pharmaceutical companies to demand more action on an agreement to publish clinical trial data.

Some FDA Scientists Feel Pressured Into Drug Approvals

Nearly one in five Food and Drug Administration scientists in a federal survey said they were pressured to approve or recommend approval for a drug despite reservations about its safety.

Half of the 400 scientists who participated in this 2002 survey by the Department of Health and Human Services' Office of Inspector General thought that scientific dissent was allowed to some extent. However, less than a third felt the work environment at FDA allowed wide leeway for differing scientific opinions related to new drug application decisions. Only 17% thought the agency had adequate procedures in place to address scientific disagreements.

Parts of the survey had originally been published in a 2003 OIG report on the effectiveness of the FDA's new drug review process. Two groups, the Union of Concerned Scientists and Public Employees for Environmental Responsibility, obtained the complete findings through the Freedom of Information Act process and recently released them to the public.

"The survey raises significant issues about drug safety and ongoing monitoring of adverse health impacts of drugs in the marketplace," said Kathleen Rest, executive director of the Union for Concerned Scientists. "The scientists' concerns warrant further investigation as Congress reviews drug approval practices at FDA."

An FDA spokeswoman did not respond to requests from this newspaper for a reaction to the survey results.

In other findings, 66% of respondents did not think FDA adequately monitored the safety of prescription drugs once they were on the market, and only 12% were completely confident that labeling decisions adequately addressed key safety concerns.

Almost 60% thought the 6 months allotted for a priority review of a drug was inadequate. The OIG in its 2003 report on the new drug application process had praised the agency for relying on expert scientific reviewers and for working collaboratively with sponsors. But even with these strengths, "workload pressures increasingly challenge the effectiveness of the review process," the report said.

—Jennifer Silverman