Erika King <EKing@phrma.org>
12/15/2003 01:02:06 PM

Record Type: Record

To: Mabel E. Echols OMB_Peer_Review/OMB/EOP@EOP

cc:
Subject: Replacement

Dr. Schwab:

With apologies, the PDF that I attached earlier this morning was missing one page. Please substitute this for the document transmitted earlier.

Erika King
Assistant General Counsel
Pharmaceutical Research and Manufacturers of America
1100 Fifteenth Street, NW
Washington, DC 20005
phone 202.835.3529
fax 202.835.3565
eking@phrma.org

- PhRMA Comments to OMB (9.15.2003) .pdf

Erika King
Assistant General Counsel

PhRMA

December 15, 2003

Dr. Margo Schwab
Office of Information and Regulatory Affairs
Office of Management and Budget
725 17th Street, N.W.
New Executive Office Building
Room 10201
Washington, DC 20503

Re: Proposed Bulletin on Peer Review and Information Quality, 68 Fed. Reg. 54023 (September 15, 2003)

Dr. Schwab:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in response to the guidelines proposed by the Office of Management and Budget (OMB) on September 15, 2003, calling for the peer review of significant scientific and technical information used by federal agencies such as the Food and Drug Administration (FDA) to formulate regulatory policies. OMB issued the proposed guidelines under the authority of section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Information Quality Act), the Paperwork Reduction Act, and Executive Order 12866. In these comments we respond to OMB's invitation to address the scope of the proposed guidelines and convey our general support for OMB's objective to promote the quality, objectivity, and reliability of information relied upon by federal agencies.

PhRMA is a voluntary, nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to discovering medicines that allow patients to lead longer, healthier, and more productive lives. In 2002 alone, PhRMA members invested an estimated $32 billion to discover and develop new medicines. PhRMA companies are the source of nearly all new drugs that are discovered and marketed throughout the world. As the leaders in the search for innovative new cures, PhRMA members hold the overwhelming majority of the new drug approvals filed with FDA. Accordingly, PhRMA and its members have a major stake in the quality of information relied upon by FDA and the efficiency of the processes that it uses to assure information reliability.

I. Purpose of the Guidelines

PhRMA understands that the purpose of OMB's proposed guidelines is to promote the quality, objectivity, and reliability of information relied upon by agencies such as

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3529• FAX: 202-835-3565 • E-Mail: eking@phrma.org

FDA to support their regulatory decisions. PhRMA and its members support this objective. We share OMB's conviction that rigorous expert review is critical to ensuring the quality of scientific studies and reports. However, just as OMB acknowledged the wide variety of federal agency functions and procedures in its Data Quality Guidelines, OMB's expectations for agency peer review should take into account the varied functions and staffing of the agencies, as well as the diverse sources of the scientific information upon which they rely.

OMB's expectations, as reflected in the proposed guidelines, appear to be consistent with this perspective. Under the proposal, federal agencies would be required to develop peer review procedures appropriate to the types of significant information they generate and rely upon, within the broader framework of the proposed guidelines. According to OMB:

> . . .[F]or significant regulatory information, the agency should select an appropriate peer review mechanism based on the novelty and complexity of the science to be reviewed, the benefit and cost implications, and any controversy regarding the science. Depending on these factors, appropriate peer review mechanisms for significant regulatory information can range from review by qualified specialists within an agency (if they reside in a separate agency program) to formal review by an independent body of experts outside the agency.[1]

II. FDA's Commitment to Peer Review

In promulgating major rules and formulating other important policies that depend on scientific findings, FDA usually does follow procedures that achieve the objectives of the proposed OMB guidelines. The agency strives to assure that critical scientific studies have been evaluated by experts independent of the agency.

A recent illustration is FDA's trans fat labeling rule.[2] The scientific information relied on by FDA to develop its trans fat labeling rule could be considered "especially significant" under the OMB proposal, since the rule could have an annual impact of $100 million or more upon important public or private sector decisions. Consequently, the information used to support this regulatory action could have been subject to OMB's peer review requirements for "especially significant scientific information." PhRMA believes that the procedures FDA followed included the key elements that would satisfy OMB's proposed guidelines.

FDA's public deliberations began in 1994 when it received a citizen petition from the Center for Science in the Public Interest (CSPI), which asserted that consumption of trans

---

1 68 Fed. Reg. at 54027.

2 68 Fed. Reg. 41434 (July 11, 2003).

III. OMB's Exemption of NDA and BLA Approvals

OMB's peer review proposal would not alter FDA's existing process for evaluating scientific information submitted by sponsors seeking FDA approval to market new drugs and biologics. This exclusion represents wise policy.

The proposed guidelines exempt information relied on in certain agency decisions, including individual adjudications and permit applications. Under the Administrative Procedure Act, "adjudication" is defined as the "agency process for the formulation of an order." "Order" is in turn defined as "the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rule making but including licensing." And "license" is defined as "the whole or a part of an agency permit, certificate, approval, registration, charter, membership, statutory exemption or other form of permission."[4]

An FDA decision to approve or deny an application to market a new drug or biologic would clearly fall within the category of "individual adjudication." And it would also qualify as "permitting." Many agency adjudications "begin with an application [for a license or permit]. Private individuals find that they cannot engage in certain conduct or activity without clearance from an administrative agency . . . In [non-formal application] processes, the applicant will first receive an administrative determination and [a] hearing will result only if the applicant chooses to challenge the result of that determination."[5]

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) leaves no doubt that FDA approval or denial of permission to market a new drug would qualify as "adjudication." The section provides for a formal adjudicatory hearing when FDA declines to approve a new drug or withdraws approval of a marketed drug.[6] Since disputes over approval of new drugs may be resolved through an adjudicatory process, FDA decisions on NDAs fall squarely within the Administrative Procedure Act's definition of "adjudication" or "licensing." Accordingly, information submitted by an applicant for approval, which in turn is used by FDA in granting or withholding approval, would not be subject to formal peer review requirements beyond those that FDA already observes in ruling on such applications.

OMB's decision to exclude individual adjudications – and thus FDA's disposition of applications to market new drug or biologics – represents sound policy for two reasons. First, OMB's proposed requirements would ill suit a process that, by law, must protect the confidentiality of proprietary research data that product sponsors must submit to the agency. Second, FDA's customary procedures for evaluating the findings of such studies provide strong assurance that the evidence on which the agency ultimately bases its decision will be of high

---

4 5 U.S.C. § 551 (2003) (emphasis added).

5 Koch, Charles, Administrative Law and Practice, Second Edition, Vol. 2, § 5.31 (1997).

6 21 U.S.C. § 355(d)-(e), (h) (2003).

quality. These procedures are the most rigorous of any in the world. Imposition of additional peer review requirements would undermine reforms that FDA and Congress have taken years to fashion in an attempt to balance the value of expeditious action with the need for caution.

First, as a general matter, FDA does not "disseminate" the preclinical and clinical research data that make up the major part of a new drug application (NDA) or biologics license application (BLA). Since FDA was first given authority to require premarket approval of new medicines, the agency has acknowledged the commercial value of this information and protected its confidentiality. This position, dictated by the FDCA as well as the Trade Secrets Act, is consistent with the Freedom of Information Act and has been upheld by the courts. Thus, to the extent that OMB's peer review proposal is designed to assure the reliability of scientific information that agencies make widely available, FDA's drug approval process is not an appropriate target.

Furthermore, the OMB proposal seems to contemplate agency decisions – perhaps chiefly dissemination decisions – involving a single, potentially decisive study or set of study findings. The typical new drug application may contain several dozen studies, first in animals and then in progressively larger populations of human subjects. Usually no one of these is decisive, and sometimes none is influential in the colloquial sense. FDA's review – and that of the outside experts it consults – focuses on the entire body of research. The agency, therefore, has constructed a process for, first, internal review and, later, external review, which allows and typically demands assessment of an entire body of work. This is not a process that could accommodate study-by-study assessment, even if all of the relevant studies could be shared publicly.

Second, taking account of these realities, FDA has devised a process of assessment that provides a very high degree of assurance that the scientific evidence on which it relies is both relevant and reliable. The process relies on the training and experience of a highly educated cadre of experts among the agency's own employees, most of whom have years of experience in evaluating clinical studies of medicines in their respective fields. It also draws on the expertise of independent consultants, most of whom are appointed to serve for extended periods on advisory committees in designated medical specialties. Finally, to the extent consistent with FDA's obligation to protect proprietary research data, the process affords opportunities for outside parties, including opponents of approval and representatives of patient groups, to know the agency's assessment, to hear the views of the advisory committee members, and to convey their own views of the relevant science before a formal agency decision is rendered.

The following bullet points summarize the key elements of the FDA process for reviewing evidence submitted in support of new medicines and for deciding whether the evidence justifies approval for marketing.

- FDA staff scientists review every study submitted as part of an NDA. This review commences with the sponsor's submission of an application to conduct clinical trials and continues through the submission of a final marketing application. Sponsors must allow FDA access not only to summaries of research findings but also to the raw data, including patient records, from each clinical trial. Not infrequently, FDA medical reviewers analyze the raw data and reconstruct the study findings.

- If FDA scientific staff are inclined to believe a drug merits approval, almost always the matter will be set for discussion before and a vote by an advisory committee whose members are experts in the relevant clinical discipline. The members of these committees are never employees of FDA. A few may work for another part of the federal health apparatus, e.g., NIH or CDC. The majority, on some committees all, of the members have no other ties to FDA. None is an employee of the product sponsor and none can have been an investigator of the product under review. Committee members are vetted for other potential conflicts of interest and excluded from participation if they or professional colleagues have ties to the product sponsor.

- Members of FDA advisory committees must be appointed in accordance with, and must operate in compliance with, the Federal Advisory Committee Act. This means that scheduling of meetings is a matter of public record; that the public is informed as to what issues or products are scheduled for discussion at a particular meeting; that the majority of committee discussion occurs in public view (save for portions set aside for discussion of trade secret information); and that the public knows what questions FDA has asked the committee members to consider and can have access to most of the materials the agency has provided the committee (again, save for trade secret information).

- Members of the public, including critics of a product or of studies of the product, may observe the discussion among advisory committee members and convey their views, both orally and in writing, to the committee (and indirectly to FDA) about the interpretation of the study results. Typically, committee members are asked to vote on the questions that the agency has asked. Committee meetings are widely attended and closely watched, not only by product sponsors but also by representatives of medical specialties and of patient groups, the investment community, and the general public.

- FDA has a meager budget for funding research and so advisory committee members have no reason to expect financial advantage from their service. Per

diem payments and reimbursement of travel expenses are the only material compensation for their service. They see their role as a professional opportunity and responsibility, not as a mechanism for private gain.

- Members of FDA's advisory committees often serve for two or three years or even longer, and thus offer advice on several products and dozens, even scores, of studies during their time of service. They are not selected to help evaluate particular products, much less individual studies. This continuity is an asset, because members soon become familiar with product development efforts and clinical experience within a discipline, which allows them to bring to bear unique experience with work in the field. With hundreds of studies, and dozens of products, to evaluate, the peer review system that FDA has fashioned would collapse if each pivotal study or each product required creation of a new (and inexperienced) cadre of experts. Indeed, in some therapeutic fields, there simply would not be sufficient expert reviewers to handle such a workload.

FDA has devised this process over many years and now relies upon it, because, among other reasons, it affords a high degree of assurance that the scientific evidence on which the agency must rely to rule on applications for approval to market medicines is relevant, reliable, and honest. Imposition of additional peer review requirements would contribute little of value and would add to the time and expense of a gatekeeper function that has historically been criticized for obstruction and delay. For this reason, we support exclusion of FDA decisions on new drug applications from the proposed OMB peer review process.

IV. Conclusion

In sum, therefore, we generally support peer review of significant scientific and technical information used by federal agencies, including FDA, to formulate regulatory policies. We believe that generally, when promulgating major rules and formulating other important policies that depend on scientific findings, FDA does follow procedures that achieve the objectives of the proposed OMB guidelines. We also support OMB's decision to exempt information relied on in adjudications and permit applications. In the particular context of FDA decisions on new drug applications and biologics license applications, peer review procedures would be ill-advised, in certain situations unlawful, and in any event unnecessary in light of FDA's procedures for evaluating the data submitted in those applications.

Respectfully,

Erika King
Assistant General Counsel
Pharmaceutical Research and Manufacturers
of America
1100 15th Street, NW
Washington, DC 20005
202.835.3529 (phone)
202.835.3565 (fax)
eking@phrma.org