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July 22, 1998

Dockets Management Branch
HFD-305 Room 1-23
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Reference is made to the June 8, 1998 publication in 63 FR 31143 of the FDA Proposed rule on Dissemination of Information on Unapproved/New Uses for Marketed Drugs. Attached are comments on the proposed rule submitted by Rhône-Poulenc Rorer Pharmaceuticals Inc.

Sincerely yours,

A handwritten signature in black ink that reads 'Kathryn A. Roberts'.

Kathryn A. Roberts
Senior Manager
Worldwide Regulatory Affairs

KAR/maf
Encl.

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RHÔNE-POULENC RORER PHARMACEUTICALS INC.

**COMMENTS ON FDA PROPOSED RULE ON DISSEMINATION OF
INFORMATION ON NEW USES (63 FR 31143)**

Submitted July 22, 1998

1. Section 99.3 of the proposed rule provides definitions for terms used within the proposed rule. Section 99.3 (g) defines "new use" as "a use that is not included in the approved labeling of an approved drug or device, or a use that is not included in the statement of intended use for a cleared device." However, in the portion of the preamble related to this section, there is a discussion of the definition of "new use" in which it is further defined as "one that would require approval or clearance of a supplemental application in order for it to be included in the product labeling." Examples are provided of what would be considered a "new use" and therefore, covered by this rule. The examples include "comparative claims to other agents for treatment of the same condition."

While a supplemental application would be submitted for any new use, the comparative data on two drugs approved for the same indication would not always be included in a product's labeling. Comparative claims for approved uses can currently be made in advertising without the comparison being included in the product labeling. The final rule should be clear that the definitions of "new use" do not include comparative claims to other agents for approved uses.

2. In the preamble for sec. 99.101, there is a discussion of reprints vs reference publications. It acknowledges that reference publications can discuss many new uses and the law could be construed to mean that a manufacturer would be required to submit a supplement for each of the many new uses mentioned. It also states that although the statute does not allow a reference publication, as a whole, to focus on the disseminating manufacturer's products or new uses, it does not prohibit a manufacturer from citing a particular use or uses in a publication that does not have such a focus.

It is possible that a reprint, although primarily discussing one use, could also mention another use that is not intended to be the subject of a supplemental application. The regulation of reprints should be the same as reference publications in this regard. Reprints that mention a new use that is not the focus of the clinical investigation should still be allowed to be disseminated if the manufacturer cites only the particular use that is the subject of the supplemental application.

Currently, textbooks may be disseminated as long as they conform to FDA's October 8, 1996 Guidance for Industry Funded Dissemination of Reference Texts. The guidance allows sponsors to disseminate reference texts provided that they: do not focus on one product, are not written or influenced by a company, are readily available in bookstores, provide a broad range of therapies and have no specific product information appended to the textbook. The proposed rule on dissemination of information on new uses should make clear that this process is still allowed.

3. Section 99.101 describes the process for disseminating information from studies conducted by another manufacturer. It specifies that the manufacturer disseminating the information must obtain permission from the manufacturer who conducted the study.

This will have the greatest impact on the dissemination of comparative studies of drugs from two different companies. To meet the requirements for dissemination of information on new uses, companies are required to provide FDA with objective and scientifically sound information pertaining to the safety or effectiveness of the new use. This is likely to include research sponsored by other manufacturers. FDA may require that this information accompany the reprint being disseminated. This creates a conflict in meeting the requirements of section 99.103 if the other manufacturer denies permission. Once a peer reviewed article is published and readily available in the public domain, no permission should be required to enable dissemination of that clinical investigation.

The strict interpretation of this section also precludes the dissemination of textbooks without obtaining the permission of every company that conducted the clinical investigations included in the reference publication.

4. Section 99.103 requires mandatory statements and information to be prominently displayed with the reprint. Included in the requirements for disclosure are "the names of any authors of the information who are employees of, or consultants to, or have received compensation from the manufacturer, or who have a significant financial interest in the manufacturer." The preamble related to this section states, "When there is a question as to whether a relationship is significant, it should be disclosed. For further guidance and direction on the disclosure of significant financial interests, manufacturers should refer to FDA's final rule on Financial Disclosure by Clinical Investigators."

The requirement for disclosure for authors “who *have* (emphasis added) a significant financial interest in the manufacturer” is inappropriate. The relevant timeframe for establishing whether a clinical investigator has significant financial ties to a manufacturer is at the time the study is being conducted. Due to the time lag between the conduct of the study and the publication of the results, the investigators’ financial interests at the time of publication are irrelevant in evaluating the potential for investigator bias. It is unreasonable and impractical to subject an investigator, at the time of study publication, to the requirements of the rule on Financial Disclosure by Clinical Investigators. The final rule should make clear that the disclosure of significant financial interest in the manufacturer is in line with the level required by the rule on Financial Disclosure and should apply only to the financial interests at the time the study was conducted and not the author’s current interests.

5. Section 99.201 describes the required information in a manufacturer’s submission to the agency prior to dissemination of information on a new use. In many cases, manufacturers will be conducting studies supporting the new use under an IND and will already have an IND on file with the Agency. An IND includes currently available information describing the new use of a marketed drug that is under investigation. In addition, the FDA reviewing division is already familiar with the data in the IND. It would greatly reduce the administrative burden on both FDA and manufacturers to allow reference to the IND for the information on the new use in order to satisfy the requirements for the manufacturer’s submission. The manufacturer’s submission could then include a reference to the IND, an updated bibliography, the certification statement and a copy of the information to be disseminated along with the mandatory statements that would accompany the reprint.

6. Section 99.201 discusses the 60 day review clock for manufacturers’ submissions. Section 99.201 (d) states that the 60 day period shall begin when FDA receives a complete submission, with completeness determined by FDA. There is no time limit for the determination of completeness. FDA should be limited to 5 working days to make that determination. If deemed complete, the 5 days should be part of the full 60 day review clock.



7. Section 99.301 describes agency action on a submission. None of the actions listed include an approval to proceed with dissemination of the reprint. FDA should be required to promptly notify the manufacturer if they approve the submission in less than 60 days.

8. Section 99.201 describes the content of the manufacturer's submission to FDA prior to disseminating the information on new uses. Included in the information required are reports of adverse experiences associated with the new use. A manufacturer should be required to report only those adverse experiences on its product that it has received directly. Companies do not have access to the details of cases submitted to other manufacturers who market a product containing the same drug substance to enable appropriate evaluation of the reports. In addition, the adverse experience information provided should be in summary or tabular form rather than individual case reports.

9. Section 99.301 outlines agency action on a submission. The review of the information in a manufacturer's submission to enable dissemination of information on new uses will require significant review time by the appropriate FDA reviewing division. Reviewing divisions are currently under time constraints to complete reviews of original NDAs and supplements in accordance with the user fee schedule. Unless FDA devotes significant new resources to dissemination submissions, reviewers are likely to give higher priority to user fee submissions, resulting in prolonged review time or inability to meet the 60 day review timeframe.

10. Section 99.401 describes corrective actions that may be taken by FDA. It states that "If FDA receives data after a manufacturer has begun disseminating information on a new use, and based on that data, determines that the new use... may not be effective or may present a significant risk to public health, FDA shall ... take appropriate action to protect the public health." FDA does provide an opportunity for a meeting with the manufacturer prior to taking action to cease dissemination of information on a new use.

In situations where a manufacturer disagrees with FDA's determination, a mechanism for independent review of the issue should be instituted in accordance with the Dispute Resolution provisions of FDAMA and the FDA rule on Internal Review of Agency Decisions published June 16, 1998.

11. Section 99.501 describes the recordkeeping and reporting requirements and includes the submission of semi annual reports. Since annual IND progress reports are already required to be submitted to the reviewing divisions for every IND, two additional reports containing redundant information is an overburdensome requirement. The semi-annual reports submitted to DDMAC should be limited to lists of articles and reference publications relating to the new use that were disseminated to a health care practitioner (HCP), and a list of categories of HCPs who received the articles and an updated bibliography.

Just as the current IND regulations allow a preparation period for annual reports, there should be time established between the period to be covered by the report and the date due to the agency.

This section also establishes that copies of all information must be maintained for 3 years after a company has ceased dissemination of such information. If the supplemental application is approved, manufacturers should no longer be required to keep the records. The requirement for recordkeeping should only apply if the supplement is not approved, or the company ceases dissemination prior to approval of the supplement.

12. Currently, when contacted by a Health Care Professional, a company's medical affairs department can discuss information on new uses of marketed products. When company representatives disseminate written information on a new use under these regulations, they should be permitted to discuss the clinical investigation with the recipient.

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CERTIFIED

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MAIL



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