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BY MESSENGER

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RE: FDAMA Phase IV Tracking

Dear Drs. Devine and Woodcock:

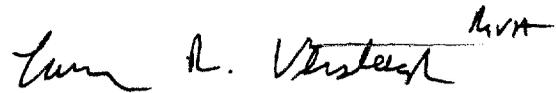
We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry input on the Phase IV Tracking provisions of the FDA Modernization Act of 1997 (FDAMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies; this year alone our member companies are expected to invest over \$20 billion in discovering and developing new medicines.

PhRMA is pleased to submit these suggestions for implementation of the FDAMA provisions or reporting on postmarketing studies, Section 130. As we note in our suggestions, this FDAMA provision is intended to provide general information to FDA and the public on the status of phase IV studies and compliance. PhRMA urges the Agency to draw on its existing programs and policies concerning postmarketing studies, including in particular those set forth at 211 C.F.R. § 314.81(b)(2)(vii) related to status reports on postmarketing studies and those set forth in Section 6010.2 of CDER's Manual of Policies and Procedures related to FDA's procedures for the tracking and review of Phase IV commitments. FDA should also specify what information a drug sponsor must include in

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reports submitted under Section 130, when such reports should be submitted, and what information in the reports will be made available to the public.

We would be happy to answer any questions that you might have about this submission on Phase IV tracking, Section 130.

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Enclosure: PhRMA's Recommended Approach for Implementation of the FDAMA Provisions for Reporting on Postmarketing Studies (§ 130)

cc: Jane Axelrad, Associate Director for Policy, CDER

June 25, 1998

**PhRMA's RECOMMENDED APPROACH TO IMPLEMENTING THE FDA
MODERNIZATION ACT'S PROVISIONS FOR REPORTING ON
POSTMARKETING STUDIES (§ 130)**

Section 130 of the FDA Modernization Act of 1997 adds a new section 506B to the Federal Food, Drug & Cosmetic Act (FFDCA) (21 U.S.C. § 356b) to require sponsors of new drugs to report to FDA on "postmarketing approval studies." As explained further below, Section 130 covers postapproval (phase IV) studies that a sponsor has agreed to conduct as a condition of a drug's approval. Other phase IV studies, which the sponsor has not agreed with FDA to conduct as a condition for drug approval, are not covered by Section 130. This provision is intended to provide general information to FDA and the public on the status of phase IV studies and compliance. In enacting the statute, Congress provided no indication that it was trying to redress any known problem regarding postapproval studies or surveillance more generally.

When FDA issues regulations to implement Section 130, as required by the FDA Modernization Act, it should draw on its existing programs and policies concerning postmarketing studies, including in particular those set forth at 21 C.F.R. § 314.81(b)(2)(vii) related to status reports on postmarketing studies in NDA annual reports and those set forth in section 6010.2 of CDER's Manual of Policies and Procedures related to FDA's procedures for the tracking and review of phase IV commitments. Although these previously existing programs are broader in scope than Section 130, Section 130 codifies the programs in general terms for phase IV study commitments made as a condition of drug approval. In order to administer all of these postapproval reporting requirements in a consistent manner and facilitate compliance,

FDA should implement Section 130 by amending its existing regulation (21 C.F.R. § 314.81(b)(2)(vii)) and guidance (MAPP 6010.2) to incorporate the new statutory reporting requirement.

Specific issues FDA should address in implementing Section 130 include confirming the scope of Section 130 and clarifying when and how Section 130 will become effective. Drawing on the existing requirements of 21 C.F.R. § 314.81(b)(2)(vii) and MAPP 6010.2, FDA should also specify what information a drug sponsor must include in reports submitted under Section 130, when such reports should be submitted, and what information in the reports will be made available to the public.

1. STUDIES COVERED BY SECTION 130

Section 130 is limited in scope. First, it only applies to studies that a drug sponsor commits to conduct pursuant to an agreement with FDA. FDCA § 506B(a)(1); 21 U.S.C. § 356b(a)(1).

Second, it only applies to studies conducted as a condition of drug approval. Section 130 does not expressly state that it applies only to studies conducted as a condition of approval; however, it clearly contemplates only covering such studies and can only make sense when read in such a manner. Most notably, Congress did not reference or incorporate the broader reporting requirements of 21 C.F.R. § 314.81(2)(vii) and MAPP 6010.2 in Section 130, demonstrating that Congress intended Section 130 to be narrower in scope. 21 C.F.R. § 314.81(2)(vii) requires the holder of an approved drug application to include in its annual report a statement on the status of "*any* postmarketing studies performed by, or on behalf of, the applicant." (emphasis added). MAPP 6010.2

applies to commitments to conduct phase IV studies, whether made before or after approval and whether made voluntarily or as a condition of approval. Section 130 contains no comparable language, indicating that Congress did not intend to cover by statute any and all postmarketing studies. The structure of Section 130 further supports this reading. Reports are due under Section 130 one year after a drug's approval. FDCA § 506B(a)(1); 21 U.S.C. § 356b(a)(1). No comparable provision exists that could be applied to determine the due date for a study agreed to after approval, illustrating that Section 130 is not intended to cover such studies.

Third, Section 130 should only apply to clinical studies (*i.e.*, human studies) that a sponsor agrees to conduct as a condition of a drug's approval, as listed in the drug approval letter pursuant to MAPP 6010.2. Section 130 is silent on this point. However, clinical studies are both the most significant phase IV commitment a sponsor might make and the type of commitment that Congress likely had in mind in requiring the tracking and publication required by Section 130. In comparison, it would not seem justified to require the same expenditure of sponsor and FDA resources to track under the formal program created by Section 130 phase IV testing such as *in vitro*, toxicology, or stability studies.

If anything, FDA should only require reporting under Section 130 on non-clinical studies related to safety that would not otherwise be reported under another postapproval reporting mechanism. Reporting could also be required for products that have been approved on an accelerated basis subject to certain post-approval conditions and commitments.

2. EFFECTIVE DATE OF SECTION 130 AND PRIOR AGREEMENTS

Section 130 provides that the sponsor of a drug shall report on the progress of studies it agrees with FDA to conduct, or the reasons for the failure of the sponsor to conduct studies, in such form as the FDA shall require by regulation. FFDC § 506B(a)(1); 21 U.S.C. § 356B(a)(1). FDA should confirm that consistent with the statutory language, Section 130 will not take effect until FDA issues implementing regulations and informs sponsors how to submit the required reports.

Once FDA issues regulations, and Section 130 takes effect, sponsors should have at least six months by which to submit progress reports for studies they previously agreed to conduct. Section 130 states that sponsors shall have six months to file progress reports for studies they agreed to prior to enactment of the FDA Modernization Act. FFDC § 506B(a)(2); 21 U.S.C. § 356b(a)(2). As clearly contemplated by the law, the six-month period must be read in conjunction with the requirement for implementing regulations. Thus, FDA should give sponsors six months from the issuance of implementing regulations for the submission of initial reports on any previously agreed to studies. If FDA provides that reporting under Section 130 should be done as part of an annual report submission, as recommended here, a sponsor would satisfy Section 130 when it files an annual report during the six-month period. If a sponsor has already filed an annual report within the previous six months containing information on phase IV study commitments, its Section 130 reporting obligation should be deemed to have been satisfied until its next

annual report is due. Requiring a sponsor to file a separate additional report under Section 130 on the heels of the NDA annual report would be duplicative and unnecessary.

In addition, FDA should set some reasonable limit on how far back it will reach in requiring sponsors to report on studies they agreed to conduct years before enactment of Section 130 but that remain open for some reason or another. For example, FDA could provide that no reporting obligation exists under Section 130 for a study agreement entered into more than three years ago.

3. CONTENT AND FORMAT OF REPORTS

As noted above, the reporting process under Section 130 can be streamlined by incorporating such reports in the annual status reports sponsors must file under an NDA pursuant to 21 C.F.R. § 314.81(b)(2)(vii). For example, FDA could amend 21 C.F.R. § 314.81(b)(2)(vii) to include a designated section on the status of phase IV study commitments entered into as a condition of drug approval.¹

Whether included in an NDA annual report or elsewhere, Section 130 only requires a sponsor to submit "a report of the progress of the study or the reasons for failure of the sponsor to conduct the study." FFDCa § 506B(a)(1); 21 U.S.C. § 356b(a)(1). Attachment C of MAPP 6010.2 provides standardized categories that capture such information, and FDA should direct sponsors to utilize standardized descriptions based on MAPP 6010.2 when making reports under Section 130. Specifically, sponsors should state for each study covered by Section 130 which of the

following status categories apply:

Study not begun

Study not begun, will begin in future

Plan and/or feasibility not yet agreed

Study in progress, underway

Study halted; decision to be reviewed with FDA

Study submitted

Company released from commitment

These general categories capture the information required by Section 130 in a uniform manner. Section 130 does not require any particular additional information. Thus, sponsors should be left to their discretion to determine what additional details to report.

4. REPORTING DEADLINES

For study agreements entered into after the effective date of Section 130, sponsors must submit progress reports within 1 year after drug approval. FFDCa § 506B(a)(1); 21 U.S.C. § 356b(a)(1). FDA should conform this reporting deadline to the required timing for NDA annual reports by providing by regulation that the Section 130 report may be submitted within 60 days of the anniversary date of the drug's approval, as permitted by 21 C.F.R. § 314.81(b)(2).

5. PUBLICLY AVAILABLE INFORMATION

¹ Holders of approved biologics licenses are not now required to submit annual reports. Accordingly, some type of separate progress report can be submitted on Phase IV commitments to satisfy Section 130 for biologics.

Section 130 directs FDA to make available to the public information identifying sponsors and establishing the status of phase IV studies for which sponsors have submitted reports under the section. FDCA §§ 506B(b)&(c); 21 U.S.C. §§ 356b(b)&(c). Section 130 explicitly limits the public release of information by providing that reported information should be considered public "to the extent that the information is necessary (1) to identify the sponsor; and (2) to establish the status of a study" FDCA § 506B(b); 21 U.S.C. §§ 356b(b). In accordance with this requirement, the only information on studies that should be considered public and released is the standardized information that a sponsor reports based on the categories contained in MAPP 6010.2 (*e.g.*, study not begun, study in progress, etc.). Section 130 requires no further release of information, and FDA should respect that statutory limitation due to the proprietary and commercially sensitive information involved.

* * *

Section 130 strengthens FDA's oversight of phase IV study commitments by codifying current reporting requirements in statute for postapproval studies entered into as a condition of drug approval. FDA can implement Section 130 in the most effective and efficient way by amending those existing regulations to incorporate Section 130.