Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

July 31, 2003

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

RE: Docket No. 2003D-0228 - Draft Guidance for Industry on Continuous Marketing Applications: Pilot 1--Reviewable Units for Fast Track Products Under the Prescription Drug User Fee Act

Dear Sir/Madam:

The following comments on the above noted draft Guidance document are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

PhRMA values the work FDA has put into the draft Guidance and appreciates the opportunity to comment. PhRMA hopes that this consolidated set of industry comments will permit FDA to meet its goal of initiating this Pilot program in October 2003.

General Comments/Statement

PhRMA commends FDA for its continued attention to innovative ways to improve the efficiency of the drug development and approval process. Specifically, we applaud FDA's agreement, under the performance goals that accompanied the June, 2002, reauthorization of the Prescription Drug User Fee Act (PDUFA goals), to formally explore the concept of the "continuous marketing application" in the form of two pilot projects. Under "Pilot 1" FDA agreed to evaluate the costs and benefits of early review of parts of a marketing application, while under "Pilot 2" the agency will evaluate the impact of frequent scientific feedback during the IND phase of drug development.

03D-0228

C 4

Specific Comments

Section II Background

1. Paragraph 2 The second paragraph states that *"These pilot programs will provide the Agency with important information regarding whether such activities can improve the efficiency of the drug development and review process and shorten review time."*

a). It is unclear what the baseline will be against which the outcome of the pilots will be measured. Statutory provisions enacted under FDAMA for "fast track" applications formally established a mechanism, albeit as FDA resources allowed, for the submission and early review of portions of an application before submission of a complete application. As stated in the draft guidance, FDA has engaged in such early review under FDAMA for many years. Will the results of Pilot 1 be assessed against FDA's historical performance with fast track application review and approval? Or will performance on Pilot 1 applications be compared with that for fast track applications not included in Pilot 1?

b). Both Section VII of the PDUFA Goals Letter and the draft guidance for Pilot 1 impose eligibility criteria for a designated fast track application to be included in Pilot 1 as well as numerous rules governing submission and review of the reviewable units (RU). Presubmission and prior review has not previously been subject to such formal rules but, instead, has been driven by the particular development program and agreements between the applicant and the review division. Whether the results from the pilot, conducted under its formal rules and restrictions, can be generalized to form a conclusion on the costs and benefits of any continuous marketing application paradigm will need careful consideration.

The agency should prospectively describe, at least in general terms, the parameters to be considered in evaluating the results of the Pilot 1, including the performance baseline(s) that will be used for comparison.

Section III. Implementation

Section III. A. Eligible NDA/BLA Applications

1. Based on a review of published Fast Track designation statistics it is unclear whether the current criteria will allow for each Division to participate in the Pilot. PhRMA recommends that a review of eligible products be conducted prior to finalizing the eligibility criteria to insure that there is wide-spread experience with this pilot.

Consideration should also be given to including appropriate supplements, to new drug/device delivery systems (e.g. pulmonary delivery), complex/new dosage forms and the like.

2. Paragraph 2 The draft guidance is vague on the process for "enrolling" an application in Pilot 1. The second paragraph states, *"Discussion between the applicant*

and review division of a potentially eligible (emphasis added) *application for Pilot 1 would occur at the end-of-phase 2 or pre-NDA or -BLA meeting…. Any agreements between the review division and the applicant with regard to participating in Pilot 1 would be finalized before submission of any reviewable units and would be documented in writing (e.g., in meeting minutes, letter to the applicant)."* However, in Section III.C. (Page 8) - *Pilot 1 Implementation - Process for Reviewable Units* the draft guidance says, *"As already noted, for eligible* (emphasis added) *applications, discussion regarding a plan for RU submissions should be undertaken at the end-of-phase 2 or pre-NDA or - BLA meeting, or at an additional meeting scheduled for this purpose."*

The implication of the statement in Section III.A. is that initial discussions of Pilot 1 eligibility would not take place until, at the earliest, the end-of-phase 2 meeting. The implication of the statement in Section III.C. is that discussions of a plan for RU submissions for eligible applications would be included at the end-of-phase 2 meeting, suggesting that a decision for enrollment in Pilot 1 could already have been made prior to that meeting or that any "eligible application" is automatically subject to Pilot 1. On the other hand, the PDUFA goals for Pilot 1 state that Pilot 1 applies to fast track designated drugs and biologics that *"…have been the subject of an End-of-Phase 2 and/or a Pre-NDA/BLA meeting,"* which suggests that such meeting would have to have been held before an application can become eligible for consideration.

PhRMA recommends that the final guidance clarify when FDA would entertain a request for participation in Pilot 1 as well as its expectation for making a decision on enrollment of the application in Pilot 1. In addition, the final guidance should include discussion of FDA's expectations with respect to including applications in Pilot 1 that are following the accelerated timeline for development described under 21 CFR, Subpart E, in which an End-of-Phase 1 meeting is held to reach agreement on the design of phase 2 studies that would provide sufficient data to support a decision on its approvability. Because these applications are unlikely to be the subject of an End-of-Phase 2 meeting, is it correct to presume their eligibility for Pilot 1 would not be addressed until the pre-NDA/BLA meeting?

3. The stated purpose of the pilot project in the PDUFA goals is to test whether providing early review can further shorten drug development and review times. Selecting applications for enrollment in Pilot 1 based on the perceived "likelihood that enrollment in the Pilot will enhance the efficiency of the review" has the potential to bias the outcome. It connotes a preconceived notion of benefit from the process the pilot is intended to test. By definition in the statute, products designated for fast track are those for serious or life-threatening conditions with the potential to address an unmet medical need; by stipulation in the PDUFA goals, such fast track products will only be eligible if they have *"demonstrated significant promise as a therapeutic advance."* We recommend against imposing further subjective criteria that may bias the results of the Pilot.

It would also be informative to include in the final guidance whether the decision for enrollment of an application in the Pilot will be made at the Division, Office, or Center level.

Section III.B. Definition of Reviewable Units

1. Paragraph 2 It is somewhat unclear whether the recommendations in the draft guidance regarding reviewable units that contain less than a complete technical section represent the only choices that can be considered by an applicant and the review division or whether a review division may agree to accept, as a reviewable unit, other submissions. In Section III.B. - (Page 4) - *Pilot 1 Implementation - Definition of Reviewable Units,* the draft guidance notes that Pilot 1 "...provides for flexibility in the definition of RUs such that a review division and applicant may agree on submission of an RU that is less than a complete technical section." It further states, *"Recommendations for potential subsections are provided for each review discipline."* However, on page 5, it states, *"FDA recommendations for subsections that can be considered for potential submission as a reviewable unit are described here for each review discipline."* The phrase "subsections that can be considered" could be interpreted to mean that these are the only subsections that can be considered; focusing on the phrase "*FDA recommendations,"* however, implies broader flexibility.

PhRMA believes the final guidance should include clear language regarding FDA's intention to allow review divisions and applicants to agree on reviewable units that may differ in content from those described in the draft guidance.

Providing for additional clarity in this regard will also help ensure that there is some consistency across Divisions as the Pilot is implemented.

Section III B.1. RU for CMC Section

1. As written, the draft guidance appears to permit a sponsor to submit a RU that is comprised of either a complete CMC technical section or a subsection comprised of drug substance information. We request that the Agency clarify its statement discouraging submission of RUs comprised of a subsection of information about the drug product; *"RUs pertaining to the drug product are not encouraged due primarily to the expected increase in review resource utilization."* This statement seems inconsistent with the spirit of flexibility with respect to a well-defined subsection of a RU that is less than a complete technical section. PhRMA does not agree that the only acceptable subsection for CMC information should be comprised of drug substance information and suggests that the guidance reflect flexibility with respect to proposals that include substantially complete CMC information for drug product as long as submission of the information provided with the complete NDA would not result in substantive reassessment of the issues addressed in the Discipline Review Letter (e.g. stability data to support a longer initial shelf life or an alternate manufacturing facility).

2. The heading *"Drug Substance Information"*(Sections 3.2.S.1 through 3.2.S.7 of

Module 3) is confusing. The word *"including"* in the heading seems to imply the bullets listed beneath will comprise only the drug substance subsections listed, but in fact list drug product related and other subsections.

PhRMA recommends that reference to the drug substance subsections should be removed from the heading and included with the other listed subsections as the first bullet. The heading should be revised to read as follows: *"Recommended Drug Substance and Drug Substance-Related RU Subsections of Complete CMC Technical Section"*. The first bullet should read as follows: *"Drug Substance Sections 3.2.S.1 through 3.2.S.7"*.

In addition, the reference in the second bullet, Section 3.2.P.2.4 appears to be in error as this subsection relates to the Drug Product Container Closure System. The correct subsection reference should be provided. An "S" should be added to the subsection reference in the first bullet. The reference should read as follows: *"(Section 2.3.S. of Module 2)"*

Section III. B.2. RU for the Nonclinical Pharmacology and Toxicology (P/T) Section

1. PhRMA suggests that there should be a provision to submit all Toxicology components except the carcinogenicity and/or juvenile toxicology studies. For some Fast Track products, particularly those involving relatively short or intermittent clinical treatment periods, the carcinogenicity studies will be rate-limiting to completion of this section of the submission. For other Fast Track products, it would not be appropriate to initiate juvenile toxicology work until most other toxicology, all reproductive toxicology studies and early efficacy studies in adults are complete; while pediatric research with the compound may be planned these nonclinical studies should not be rate-limiting to submission of the NDA for adults.

Section III. B. 6. Statistical Section

PhRMA recommends changing the heading of this section to "Statistical Evaluations of Data" to clarify this section is not referring to a single complete section of the NDA/BLA.

Section III. C. Process for Reviewable Units

Section III. C. 1. Terms and Conditions for Submission of RU

1. Paragraph 1 The draft guidance provides for discussion of a plan for submission of the RUs either during the End-of-Phase 2, pre NDA/BLA meeting or at an additional meeting. If this discussion is held during a "non-entitled" meeting, the guidance should specify that the same timeframes as a Type B meeting should apply.

2. Paragraph 2 The draft guidance states that a plan for RU content and submission sequence should be documented in the meeting minutes or in a separate letter from the review division to the applicant. In this context, it notes, "*The documentation should also reference conditions under which the review division will* ***not*** *review an RU under the terms of Pilot 1 (e.g., if the applicant exceeds the number of agree-to RUs, submits*

unacceptable RUs, and/or fails to meet the projected timelines for RU submissions)." In view of the conditions for participation in Pilot 1 described in the PDUFA goals and the draft guidance, and the agreements between the review division and the applicant that will be reached, the need to stipulate conditions under which the review division will not review an RU is unclear. The statutory provision for early review of portions of a market application requires applicants to submit a schedule for the submission of the information to complete an application, the PDUFA goals provide for an agreement between the FDA and sponsor to accept "one or more" reviewable units in advance of submission of the full application, and the draft guidance, if finalized, requests documentation of the agreement to describe the total number of RUs to be submitted, the content of each, and the projected dates for submission. Clearly, submissions that fall outside of these criteria do not meet the agreement. Furthermore, under Section III.C.2 *(Submission and Filing)* the draft guidance states that an RU may not be accepted if it fails to meet the specifications of the terms and conditions agreed upon by the review division and the applicant, or if the RU is otherwise determined to be incomplete or lacking merit for review (page 9).

Unless it is FDA's intent to simply refuse review under certain circumstances, PhRMA believes that the existing statement in the draft guidance describing the conditions for not filing an RU adequately address FDA's prerogative not to review RU submissions that fall outside the terms of the agreement between the sponsor and the review division. However, it would be helpful if FDA could address, in the final guidance, whether it intends to work with sponsors in the event that a reviewable unit is determined not to be reviewable as submitted (amendments to the original agreement or amending the RU if it was determined to be incomplete during the initial filing review). Pilot 1 applications are, after all, fast track applications and, therefore, they represent potentially significant new products intended to address unmet medical needs for serious or life-threatening conditions. It is important not to lose sight of the objective of the statutory fast track provision *("The Secretary shall...facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening conditions....")* in the process of conducting the Pilot.

3. Paragraph 4 It is unclear why the Pilot proposes limiting the number of RUs per application to four. The draft guidance discusses six application subsections for possible RU submissions. PhRMA recognizes that it would be inappropriate to submit complete RUs for each one of these sections; however it should be recognized that an applicant may submit, with the agreement of the Division, some information in each of the RU areas.

Section III. C. 1. and III. C. 2. Terms and Conditions for Submission of RU and Submission and Filing

1. The draft guidance recommends certain restrictions on the number of RUs and the time frame for their submission. Specifically, it states that, generally, no more than 1 RU should be submitted for review for each technical review section and, generally no

more than 4 RUs would be accepted and reviewed under Pilot 1 for a single marketing application. In addition, it says that the submission of RU's for a given application should not generally begin earlier than 1 year in advance of the applicant's anticipated date of submission of the complete marketing application.

If the purpose of the pilot is to provide useful information on the value (costs and benefits) of early review of applications, it may produce more useful information if the guidance is less restrictive on the number and timing of submission of RUs. If restrictions imposed by the guidance result in a sample of applications that vary little from each other in this respect, the results of the pilot will provide no insight regarding whether the value of early review varies with the number or timing of RU submissions.

Section III. C.2. Submission and Filing

1. Paragraph 3 Since the Drug User Fee is to be provided at the time of submission of the first RU, we believe it is important that the guidance specify that a negative FDA determination regarding the specifications or terms previously agreed for a specific RU does not constitute a Refuse to File (RTF) decision as relates to surrender of a portion of the user fee.

2. Paragraph 3 The fast track provisions of FDAMA require the applicant to submit the user fee for the application before review of a portion of a marketing application can commence. The PDUFA goals require FDA to conduct a filing review of a reviewable unit similar to that performed on an NDA/BLA (PDUFA goal VII (A)(3)). The draft guidance states the circumstances under which an RU may not be accepted (failure to meet terms and conditions agreed upon or incomplete RU).

The final guidance should describe how the fee will be handled in the event that the initial RU submission is determined not to be filable, including the way the agency would handle the user fee if the initial RU is not filed in one fiscal year and the first filable RU is submitted in the next fiscal year.

3. Paragraph 4 The guidance indicates that the Agency will make a determination within 60 days of its findings regarding the acceptability of the RU for review. In the event FDA determines that the RU is not substantially complete for review, FDA should inform the applicant in its deficiency notice of the specific reasons for its decision, i.e. how did the RU fail to meet the specifications or terms previously agreed? Further, we suggest that the guidance reflect that the RU may be resubmitted (and the review target of 6 months applies) upon successful resolution of the deficiencies.

4. The agency should clarify that during the 6-month review clock for an RU the review clock will not be stopped if an Information Request letter is issued (per the November 2001 Guidance on Information Request and Discipline Review Letters).

5. Since this Guidance provides for a likely 3-month extension to the review clock for a major amendment to an RU, it should follow that a response from the applicant to a Discipline Review Letter would start a review clock of no more than 3 months.

6. Electronic submissions should be addressed briefly in the guidance, with particular attention to potential issues created by submission of separate RU's. For instance, if an RU contains electronic links to a technical section that will be submitted at a later date (e.g., pharm/tox section with links to the clinical section), how does FDA want this to be ultimately reconciled?

Section III. C. 3. Process for Reviewable Units - Review Considerations.
1. Paragraphs 1 and 2 The guidance should be revised to provide additional clarity regarding what constitutes a minor and a major amendment to an RU. For example, how much new information may be submitted in response to a question? And would any unsolicited update, including those provided to correct an error or omission found post-submission, be considered a major amendment?

2. Paragraph 3 The third paragraph under subsection 3 notes that any resubmission or amendment to an RU submitted by the applicant in response to an FDA discipline review letter will not be subject to the review timelines of Pilot 1 and that any review of such submissions prior to receipt of the complete application will only occur as resources allow. While it is clear that this provision addresses amendments and resubmissions following the review of an RU and receipt of a discipline review letter, the draft guidance does not address how resubmissions or amendments to an RU that is found unacceptable for filing will be handled.

The guidance should describe how FDA intends to handle resubmissions of and amendments to RUs it has found unacceptable for filing. Specifically, if the recommended restrictions on the number of RU's per discipline and application are retained, would resubmission of an amended RU that was submitted to replace an RU that was not filed be counted as submission of a second RU? Would a resubmitted RU following refusal to file be reviewed on a 6 month clock or would it be reviewed only as resources allow?

3. Paragraph 5 This paragraph states in part: "*Once accepted for review by FDA, review of an RU will continue and will result in the issuance of a discipline review letter, unless the RU is withdrawn by the applicant or the applicant's participation is terminated by the review division* (emphasis added) *(e.g., due to applicant's failure to fulfill the terms and conditions agreed to by the review division).*"

Further clarification of the basis for "termination" of participation by the review division should be provided, including discussion of the implications for the continued review of the fast track application. The guidance should describe whether applicants will be given prior warning of FDA's determination of their failure to fulfill terms of the

agreement and/or their opportunity to rectify deficiencies. Discussion of the implications, if any, for the continued review of the application under fast track should also be provided. The opportunity for review of the decision at a higher level within the Center should be made available to sponsors confronted with termination of participation.

Section III. C. 4. Process for Reviewable Units Discipline Review Letter

1. Paragraph 1 This section states that only one Discipline Review Letter will be issued for each RU. The Guidance should be revised to acknowledge that there may be more than one discipline review letter. The Guidance should also acknowledge that responses can be minor amendments with appropriately shorter review times.

2. Paragraph 1 It is understood that the Discipline Review Letter reflects preliminary feedback on the RU from the discipline review team, rather than definitive decisions relevant to the NDA or BLA from the signatory review Division or Office. However, we suggest that the guideline reflect some assurance that changes in personnel on a discipline review team subsequent to the issuance of a Discipline Review Letter would not form the basis for a *de novo* review of the RU resulting in substantive disparities between the DSL and the Agency's complete response letter.

3. Paragraph 1 Some involvement from the Division in the creation of the Discipline Review letter could improve the value of the communication and help avoid unnecessary work on the part of the Sponsor and the Division.

PhRMA recommends inclusion of a statement that aspects of the discipline review letter may be reviewed with Division and/or Office management as appropriate, while still recognizing the discipline review letter will not, even in those cases, represent definitive decisions relevant to the NDA or BLA.

4. Paragraph 2 The second sentence in paragraph 2 in subsection 4 states: *"In rare instances, the issuance of a Discipline Review Letter may be delayed beyond the PDUFA Goal date pending presentation of the NDA or BLA to an advisory committee."*

This statement is confusing. As currently written, it appears to indicate that FDA may miss the PDUFA goal date on a Pilot 1 application that it intends to present to an advisory committee. Under the PDUFA goals, FDA committed to "review and act on" applications within certain time frames. The term *"review and act on"* is *"understood to mean the issuance of a complete action letter,"* which, if it is not an approval, will *"set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval."* Delay of a discipline review letter beyond the PDUFA Goal date would be of little consequence if FDA had issued a complete action letter within the goal date because, by definition, the complete action letter would contain information from review of the RU making the discipline review letter superfluous.

PDUFA Goal VII(A)(8) also addresses the relationship between issuance of a discipline review letter and presentation of an application to an advisory committee as follows:

> *"If an application is to be presented to an advisory committee, the final DRL on the 'reviewable unit' may be deferred pending completion of the advisory committee meeting and internal review and consideration of the advice received."*

PhRMA believes the statement in the draft guidance may have intended to indicate that the discipline review letter may be delayed beyond the review clock for the RU, not the PDUFA Goal date for the application, pending presentation of the NDA or BLA to an advisory committee.

This statement regarding delay of a discipline review letter beyond the PDUFA Goal date requires clarification.

5. Currently, when an application is under review and certain questions arise that need clarification, review divisions communicate questions to the company (information requests), the questions are answered promptly, and the review continues. The description of the review process for reviewable units describes only completion of the review and the issuance of a discipline review letter. It is unclear whether FDA intends to make requests for information during the course of the review of a RU.

Questions of the type that would normally be conveyed to an applicant during the course of the review and be answered in the form of a minor amendment should continue to be communicated to sponsors of applications under Pilot 1 as information requests. Evaluation of the results of the pilot will be more informative if review practices in Pilot 1 are similar to review practices for non-pilot applications. Furthermore, the prospect of loss of these important communications may be a disincentive for sponsors to participate in Pilot 1.

Section III. D. Pilot I Timeline and Evaluation

1. Paragraph 3 The Guidance should be revised to include a statement that the independent expert consultant will protect the confidentiality of the applicant's information.

2. Paragraph 4 The CMA Pilots were developed under PDUFA III as a means to further shorten drug development and review times. As PDUFA will next be reauthorized in 2006, feedback on the CMA Pilots as currently designed will not be available for incorporation into PDUFA reauthorization discussions. PhRMA encourages the Agency to reconsider the timing of the consultant report with a goal of having at least preliminary feedback on the Pilots available no later than the end of

calendar year 2005.

3. Paragraph 4 It would be helpful to note that the report will fully reflect the applicant's feedback in addition to fully reflecting input from FDA.

Other Comments
PhRMA notes that neither this draft guidance nor the draft guidance for Pilot 2 (Draft Guidance for Industry on Continuous Marketing Applications: Pilot 2 -- Scientific Feedback and Interactions During Development of Fast Track Products Under the Prescription Drug User Fee Act - 68 FR 35901, June 17, 2003) indicates whether applications enrolled in Pilot 2 (scientific feedback) will be eligible (or, perhaps given preference) for enrollment in Pilot 1 (early review). We believe that, if circumstances permit, important information may be gleaned from evaluating the results of exposure of applications to both continuous marketing application projects.

PhRMA hopes that these comments are useful to FDA as the Agency moves forward to finalize this guidance. Please do not hesitate to contact me if there are any questions.

Sincerely,