THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUN - 4 2002

The Honorable W.J. "Billy" Tauzin
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Chairman Tauzin:

As you are aware, the Prescription Drug User Fee Act of 1992 (PDUFA), as reauthorized by the Food and Drug Administration Modernization Act of 1997, expires at the end of Fiscal Year 2002. Under PDUFA, the additional revenues generated from fees paid by the pharmaceutical and biological prescription drug industries have been used to expedite the process for the review of prescription drugs, in accordance with performance goals that were developed by the Food and Drug Administration (FDA) in consultation with PDUFA stakeholders.

FDA has worked with various stakeholders, including representatives from consumer, patient, and health provider groups, and the pharmaceutical and biological prescription drug industries, to develop a reauthorization proposal for PDUFA that would build upon and enhance the success of the program. Title 5, Subtitle A, of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, as passed by the House on May 22, 2002, and by the Senate on May 23, 2002, reflects the fee mechanisms and other improvements developed in these discussions. The performance goals referenced in Section 502 are specified in the enclosure to this letter, entitled "PDUFA Reauthorization Performance Goals and Procedures." I believe they represent a realistic projection of what FDA can accomplish with industry cooperation and both the additional resources identified in the bill and annual FDA appropriations that fully cover the costs of pay and inflation increases for the drug and biologics review process each year.

This letter and the enclosed goals document pertain only to Title 5, Subtitle A (Prescription Drug User Fees) of H.R. 3448, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. OMB has advised that there is no objection to the presentation of these views from the standpoint of the Administration's program. We appreciate the support of you and your staffs, the assistance of other Members of the Committee, and that of the Appropriations Committees, in the reauthorization of this vital program.

Sincerely,

Tommy Thompson

Enclosure

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUN - 4 2002

The Honorable Judd Gregg
Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Senator Gregg:

As you are aware, the Prescription Drug User Fee Act of 1992 (PDUFA), as reauthorized by the Food and Drug Administration Modernization Act of 1997, expires at the end of Fiscal Year 2002. Under PDUFA, the additional revenues generated from fees paid by the pharmaceutical and biological prescription drug industries have been used to expedite the process for the review of prescription drugs, in accordance with performance goals that were developed by the Food and Drug Administration (FDA) in consultation with PDUFA stakeholders.

FDA has worked with various stakeholders, including representatives from consumer, patient, and health provider groups, and the pharmaceutical and biological prescription drug industries, to develop a reauthorization proposal for PDUFA that would build upon and enhance the success of the program. Title 5, Subtitle A, of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, as passed by the House on May 22, 2002, and by the Senate on May 23, 2002, reflects the fee mechanisms and other improvements developed in these discussions. The performance goals referenced in Section 502 are specified in the enclosure to this letter, entitled "PDUFA Reauthorization Performance Goals and Procedures." I believe they represent a realistic projection of what FDA can accomplish with industry cooperation and both the additional resources identified in the bill and annual FDA appropriations that fully cover the costs of pay and inflation increases for the drug and biologics review process each year.

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Sincerely,

Tommy Thompson

Enclosure

ENCLOSURE

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the reauthorization of the prescription drug user fee program in the [cite statute] are summarized as follows:

I. REVIEW PERFORMANCE GOALS - FISCAL YEAR 2003 THROUGH 2007

A. NDA/BLA Submissions and Resubmissions:

Review and act on 90 percent of standard original NDA and BLA submissions filed during fiscal year within 10 months of receipt.

1. Review and act on 90 percent of priority original NDA and BLA submissions filed during fiscal year within 6 months of receipt.
2. Review and act on 90 percent of Class 1 resubmitted original applications filed during fiscal year within 2 months of receipt.
3. Review and act on 90 percent of Class 2 resubmitted original applications filed during fiscal year within 6 months of receipt.

Original Efficacy Supplements:

1. Review and act on 90 percent of standard efficacy supplements filed during fiscal year within 10 months of receipt.
2. Review and act on 90 percent of priority efficacy supplements filed during fiscal year within 6 months of receipt.

Resubmitted Efficacy Supplements:

Fiscal Year 2003:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2003 within 6 months of receipt and review and act on 30 percent within 2 months of receipt.
2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements filed during fiscal year 2003 within 6 months of receipt.

Fiscal Year 2004:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2004 within 4 months and review and act on 50 percent within 2 months of receipt.
2. Review and act on 90 percent of Class 2 resubmitted original applications filed during fiscal year 2000 within 6 months of receipt.

Fiscal Year 2005:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2005 within 4 months of receipt and review and act on 70 percent within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Fiscal Year 2006

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2006 within 4 months of receipt and review and act on 80 percent within 2 months of receipt.
2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Fiscal Year 2007:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2007 within 2 months of receipt.
2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Original Manufacturing Supplements:

1. Review and act on 90 percent of manufacturing supplements filed during fiscal year within 6 months of receipt and review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

These review goals are summarized in the following tables:

ORIGINAL and RESUBMITTED NDAs/BLAs:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Applications	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmissions	90% IN 2 MO	90% IN 2 MO
Class 2 Resubmissions	90% IN 6 MO	90% IN 6 MO

ORIGINAL and RESUBMITTED EFFICACY SUPPLEMENTS:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Efficacy Supplements	90% In 10 MO	90% IN 6 MO

RESUBMITTED EFFICACY SUPPLEMENTS

SUBMISSION COHORT	CLASS 1	CLASS 2
FY 2003	90% IN 6 MO/30% IN 2 MO	90% IN 6 MO
FY 2004	90% IN 4 MO/50% IN 2 MO	90% IN 6 MO
FY 2005	90% IN 4 MO/70% IN 2 MO	90% IN 6 MO
FY 2006	90% IN 4 MO/80% IN 2 MO	90% IN 6 MO
FY 2007	90% IN 2 MO	90% IN 6 MO

MANUFACTURING SUPPLEMENTS

SUBMISSION COHORT	MANUFACTURING SUPPLEMENTS NO PRIOR APPROVAL ("CHANGES BEING EFFECTED" OR "30-DAY SUPPLEMENTS")	MANUFACTURING SUPPLEMENTS THAT DO REQUIRE PRIOR APPROVAL

FY 2003 – 2007	90% IN 6 MO	90% IN 4 MO

II. NEW MOLECULAR ENTITY (NME) PERFORMANCE GOALS

A. The performance goals for standard and priority original NMEs in each submission cohort will be the same as for all of the original NDAs (including NMEs) in each submission cohort but shall be reported separately.

B. For biological products, for purposes of this performance goal, all original BLAs will be considered to be NMEs.

III. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

1. Procedure: Within 14 calendar days of the Agency's receipt of a request from industry for a formal meeting (i.e., a scheduled face-to-face, teleconference, or videoconference) CBER and CDER should notify the requester in writing (letter or fax) of the date, time, and place for the meeting, as well as expected Center participants.

2. Performance Goal: FDA will provide this notification within 14 days for 90% in FY 2003 - 2007.

B. Scheduling Meetings

1. Procedure: The meeting date should reflect the next available date on which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested. If the requested date for any of these types of meetings is greater than 30, 60, or 75 calendar days (as appropriate) from the date the request is received by the Agency, the meeting date should be within 14 calendar days of the date requested.

Type A Meetings should occur within 30 calendar days of the Agency receipt of the meeting request.

Type B Meetings should occur within 60 calendar days of the Agency receipt of the meeting request.

Type C Meetings should occur within 75 calendar days of the Agency receipt of the meeting request.

2. Performance goal: 90% of meetings are held within the timeframe (based on cohort year of request) from FY 03 to FY 07.

C. Meeting Minutes

1. Procedure: The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail.

2. Performance goal: 90% of minutes are issued within 30 calendar days of date of meeting (based on cohort year of meeting) in FY 03 to FY 07.

D. Conditions

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) should be submitted to the review division; and

2. The letter should provide:

   a. A brief statement of the purpose of the meeting;

   b. A listing of the specific objectives/outcomes the requester expects from the meeting;

   c. A proposed agenda, including estimated times needed for each agenda item;

   d. A listing of planned external attendees;

   e. A listing of requested participants/disciplines representative(s) from the Center;

   f. The approximate time that supporting documentation (i.e., the "backgrounder") for the meeting will be sent to the Center (i.e., "x" weeks prior to the meeting, but should be received by the Center at least 2 weeks in advance of the scheduled meeting for Type A meetings and at least 1 month in advance of the scheduled meeting for Type B and Type C meetings); and

3. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for a "Type B" meeting will be honored except in the most unusual circumstances.

IV. CLINICAL HOLDS

A. Procedure: The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response.

B. Performance goal: 90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response in FY 03 to FY07 (cohort of date of receipt).

V. MAJOR DISPUTE RESOLUTION

A. Procedure: For procedural or scientific matters involving the review of human drug applications and supplements (as defined in PDUFA) that cannot be resolved at the divisional level (including a request for reconsideration by the Division after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal in FY 03 to FY 07.

C. Conditions

1. Sponsors should first try to resolve the procedural or scientific issue at the Division level. If it cannot be resolved at that level, it should be appealed to the Office Director level (with a copy to the Division Director) and then, if necessary, to the Deputy Center Director or Center Director (with a copy to the Office Director).

2. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either deny or grant the appeal.

3. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take in order to persuade the Agency to reverse its decision.

4. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the "response" should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

5. In these cases, once the required information is received by the Agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either deny or grant the appeal.

6. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions

the sponsor might take in order to persuade the Agency to reverse its decision.

7. N.B. If the Agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting in order to allow conformance with advisory committee administrative procedures.

VI. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

A. Procedure: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the agency will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

1. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., is the dose range in the carcinogenicity study adequate, considering the intended clinical dosage; are the clinical endpoints adequate to support a specific efficacy claim).

2. Within 45 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

3. Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim. (For such Phase 3 protocols to qualify for this comprehensive protocol assessment, the sponsor must have had an end of Phase 2/pre-Phase 3 meeting with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.)

4. N.B. For products that will be using Subpart E or Subpart H development schemes, the Phase 3 protocols mentioned in this paragraph should be construed to mean those protocols for trials that will form the primary basis of an

efficacy claim no matter what phase of drug development in which they happen to be conducted.

5. If a protocol is reviewed under the process outlined above and agreement with the Agency is reached on design, execution, and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the Agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

B. Performance goal: 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes (based on cohort year of request) from FY 03 to FY 07.

VII. CONTINOUS MARKETING APPLICATION

To test whether providing early review of selected applications and additional feedback and advice to sponsors during drug development for selected products can further shorten drug development and review times, FDA agrees to conduct the following two pilot programs:

A. Pilot 1 – Discipline Review Letters for Pre-Submitted "Reviewable Units" of NDAs/BLAs

1. This pilot applies to drugs and biologics that have been designated to be Fast Track drugs or biologics, pursuant to section 112 of the FDA Modernization Act (21 U.S.C. 506), have been the subject of an End-of-Phase 2 and/or a Pre-NDA/BLA meeting, and have demonstrated significant promise as a therapeutic advance in clinical trials.
2. For drugs and biologics that meet these criteria, FDA may enter into an agreement with the sponsor to accept pre-submission of one or more "reviewable units"of the application in advance of the submission of the complete NDA/BLA.
3. If following an initial review FDA finds a "reviewable unit" to be substantially complete for review (i.e., after a "filing review" similar to that performed on an NDA/BLA), FDA will initiate a review clock for the complete review of the "reviewable unit" of the NDA/BLA. The review clock would start from the date of receipt of the "reviewable unit."
4. To be considered fileable for review under paragraph 3, a "reviewable unit" must be substantially complete when submitted to FDA. Once a "reviewable unit" is "filed" by FDA, except as provided in paragraph 5 below, only minor information amendments submitted in response to FDA inquiries or requests and routine stability and safety updates will be considered during the review cycle.
5. Major amendments to the "reviewable unit" are strongly discouraged. However, in rare cases, and with prior agreement, FDA may accept and consider for review a major amendment to a "reviewable unit." To accommodate these rare cases, a major amendment to a "reviewable unit" submitted within the last three months of a 6-month review cycle may, at FDA's discretion, trigger a 3-month extension of the review clock for

the "reviewable unit" in question. In no case, however, would a major amendment be accepted for review and the review clock for the "reviewable unit" extended if the extended review clock for the "reviewable unit" exceeded the review clock for the complete NDA/BLA. (See paragraph 10 below).

6. After completion of review of the "reviewable unit" of the NDA/BLA by the appropriate discipline review team, FDA will provide written feedback to the sponsor of the review findings in the form of a discipline review letter (DRL).
7. The DRL will provide feedback on the individual "reviewable unit" from the discipline review team, and not final, definitive decisions relevant to the NDA/BLA.
8. 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.
9. The following performance goals will apply to review of "reviewable units" of an NDA/BLA for Fast Track drugs and biologics that are submitted in advance of the complete NDA/BLA under this pilot program:
   a. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 30% of "reviewable units" submitted in FY04;
   b. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 50% of "reviewable units" submitted in FY05;
   c. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 70% "reviewable units" submitted in FY06, and
   d. Discipline review team review of a "reviewable unit: for a Fast Track drug or biologic will be completed and a DRL letter issued within 6 months of the date of the submission for 90% of "reviewable units" submitted in FY07.
10. If the complete NDA/BLA is submitted to FDA while a 6-month review clock for a "reviewable unit" is still open, FDA will adhere to the timelines and performance goals for both the "reviewable unit" and the complete NDA/BLA. For example, if a "reviewable unit" is submitted in January and the complete NDA/BLA is submitted in April, the review goal for the "reviewable unit" will be July and the review goal for the complete NDA/BLA will be October.
11. Any resubmission or amendment of a "reviewable unit" submitted by the sponsor in response to an FDA discipline review letter will not be subject to the review timelines and performance goals proposed above. FDA review of such resubmissions and amendments in advance of submission of the complete NDA/BLA will occur only as resources allow.
12. This pilot program is limited to the initial submission of an NDA/BLA and is not applicable to a resubmission in response to an FDA complete response letter following the complete review of an NDA/BLA.
13. Guidance: FDA will develop and issue a joint CDER/CBER guidance on how it intends to implement this pilot program by September 30, 2003. The guidance will describe the principles, processes, and procedures that will be followed during the pilot program. The guidance also will define what subsections of a complete technical section would be considered an acceptable "reviewable unit" for pre-submission and review and how many individual "reviewable units" from one or more technical sections of an NDA/BLA can be pre-submitted and reviewed subject to separate review clocks under this program at any given time. The pilot program will be implemented in FY 2004, after the final guidance is issued and will continue through FY 2007.

B. Pilot 2 – Frequent Scientific Feedback and Interactions During Drug Development

1. This pilot applies to drugs and biologics that have been designated to be Fast Track drugs or biologics pursuant to section 112 of the FDA Modernization Act (21 U.S.C. 508), that are intended to treat serious and/or life-threatening diseases, and that have been the subject of an end-of-phase 1 meeting. The pilot program is limited to one Fast Track product in each CDER and CBER review division over the course of the pilot program.
2. For drugs and biologics that meet these criteria, FDA may enter into an agreement with the sponsor to initiate a formal program of frequent scientific feedback and interactions regarding the drug development program. The feedback and interactions may take the form of regular meetings between the division and the sponsor at appropriate points during the development process, written feedback from the division following review of the sponsor's drug development plan, written feedback from the division following review of important new protocols, and written feedback from the division following review of study summaries or complete study reports submitted by the sponsor.
3. Decisions regarding what study reports would be reviewed as summaries and what study reports would be reviewed as complete study reports under this pilot program would be made in advance, following discussions between the division and the sponsor of the proposed drug development program. In making these decisions, the review division will consider the importance of the study to the drug development program, the nature of the study, and the potential value of limited (i.e., based on summaries) versus more thorough division review (i.e., based on complete study reports).
4. Guidance: FDA will develop and issue a joint CDER/CBER guidance on how it intends to implement this pilot program by September 30, 2003. The guidance will describe the principles, processes, and procedures that will be followed during the pilot program. The pilot program will be implemented in FY 2004, after the final guidance is issued and will continue through FY 2007. The full (unredacted) study report will be provided to the FDA Commissioner and a version of the study report redacted to remove confidential commercial information or other information exempt from disclosure, will be made available to the public.

C. Evaluation of the Pilot Programs

1. In FY 2004, FDA will contract with an outside expert consultant(s) to evaluate both pilot programs.
2. The consultant(s) will develop an evaluation study design that identifies key questions, data requirements, and a data collection plan, and conduct a comprehensive study of the pilot programs to help assess the value, costs, and impact of these programs to the drug development and review process. A preliminary report will be generated by the consultant by the end of FY06.

VIII. PRE- AND PERI-NDA/BLA RISK MANAGEMENT PLAN ACTIVITIES

a. **Submission and Review of pre-NDA/BLA meeting packages:** A pre-NDA/BLA meeting package may include a summary of relevant safety information and industry questions/discussion points regarding proposed risk management plans and discussion of the need for any post-approval risk management studies. The elements of the proposal may include:

1. assessment of clinical trial limitations and disease epidemiology
2. assessment of risk management tools to be used to address known and potential risks

3. suggestions for phase 4 epidemiology studies, if such studies are warranted
4. proposals for targeted post-approval surveillance (this would include attempts to quantify background rates of risks of concern and thresholds for actions)

The pre-NDA/BLA meeting package will be reviewed and discussed by the review divisions as well as the appropriate safety group in CDER or CBER.

b. **Pre-NDA/BLA meeting with industry:** This meeting may include a discussion of the preliminary risk management plans and proposed observational studies, if warranted, as outlined above. Participants in this meeting will include product safety experts from the respective Center. The intent of these discussions will be for FDA to get a better understanding of the safety issues associated with the particular drug/biologic and the proposed risk management plans, and to provide industry with feedback on these proposals so that they can be included in the NDA/BLA submission. It is the intent of this proposal that such risk management plans and the discussions around them would focus on specific issues of concern, either based on already identified safety issues or reasonable potential focused issues of concern.

c. **Review of NDA/BLA:** The NDA/BLA submitted by industry may include the proposed risk management tools and plans, and protocols for observational studies, based on the discussions that began with the pre-NDA/BLA meeting, as described above, and may be amended as appropriate to further refine the proposal. These amendments would not normally be considered major amendments. Both the review division and the appropriate safety group will be involved in the review of the application and will try to communicate comments regarding the risk management plan as early in the review process as practicable, in the form of a discipline review letter. Items to be included in the risk management plan to assure FDA of the safety and efficacy of the drug or biologic are to be addressed prior to approval of an application. The risk management plan may contain additional items that can be used to help refine the risks and actions (e.g., background rates and observational studies) and these items may be further defined and completed after approval in accordance with time frames agreed upon at the time of product approval.

d. **Peri-Approval Submission of Observational Study Reports and Periodic Safety Update Reports (PSURs):** For NDA/BLA applications, and supplements containing clinical data, submitted on or after October 1, 2002, FDA may use user fees to review an applicant's implementation of the risk management plan for a period of up to two years post-approval for most products and for a period of up to three years for products that require risk management beyond standard labeling (e.g., a black box or bolded warning, medication guide, restricted distribution). This period is defined for purposes of the user fee goals as the peri-approval period. Issues that arise during implementation of the risk management plan (e.g., whether the plan is effective) will be reported to FDA either in the form of a PSUR or in a periodic or annual report (21 CFR 314.80 and 314.81) (ICH Guidance E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs) and addressed during the peri-approval period through discussions between the applicant and FDA. PSURs may be submitted and reviewed semi-annually for the first two or three years post approval to allow adequate time for implementation of risk management plans.

For drugs approved under PDUFA III, FDA may use user fees to independently evaluate product utilization for drugs with important safety concerns, using drug utilization databases, for the first three years post approval. The purpose of such utilization evaluations is to evaluate whether these products are being used in a safe manner and to work pro-actively with companies during the peri-approval period to accomplish this.

FDA will allocate $70,900,000 in user fees over 5 years to the activities covered in this section. FDA will track the specific amounts of user fees spent on these activities and will include in its annual report to Congress an accounting of this spending.

e. **Guidance Document Development:** By the end of Fiscal Year 04, CDER and CBER will jointly develop final guidance documents that address good risk assessment, risk management, and pharmacovigilance practices.

IX. INDEPENDENT CONSULTANTS FOR BIOTECHNOLOGY CLINICAL TRIAL PROTOCOLS

A. Engagement of Expert Consultant: During the development period for a biotechnology product, a sponsor may request that FDA engage an independent expert consultant, selected by FDA, to participate in the Agency's review of the protocol for the clinical studies that are expected to serve as the primary basis for a claim.

B. Conditions

1. The product must be a biotechnology product (for example, DNA plasmid products, synthetic peptides of fewer than 40 amino acids, monoclonal antibodies for in vivo use, and recombinant DNA-derived products) that represents a significant advance in the treatment, diagnosis or prevention of a disease or condition, or have the potential to address an unmet medical need;
2. The product may not have been the subject of a previously granted request under this program;
3. The sponsor must submit a written request for the use of an independent consultant, describing the reasons why the consultant should be engaged (e.g., as a result of preliminary discussions with the Agency the sponsor expects substantial disagreement over the proposed protocol); and
4. The request must be designated as a "Request for Appointment of Expert Consultant" and submitted in conjunction with a formal meeting request (for example, during the end-of-Phase II meeting or a Type A, meeting).

C. Recommendations for Consultants: The sponsor may submit a list of recommended consultants for consideration by the Agency. The selected consultant will either be a special government employee, or will be retained by FDA under contract. The consultant's role will be advisory to FDA and FDA will remain responsible for making scientific and regulatory decisions regarding the clinical protocol in question.

D. Denial of Requests: FDA will grant the request unless the Agency determines that engagement of an expert consultant would not serve a useful purpose (for example it is clearly premature). FDA will engage the services of an independent consultant, of FDA's choosing, as soon as practicable. If the Agency denies the request, it will provide a written rationale to the requester within 14 days of receipt.

E. Performance Goal Change: Due to the time required to select and screen the consultant for potential conflicts of interest and to allow the consultant sufficient time to review the scientific issues involved, the performance goals for scheduling the formal meeting (see section III) may be extended for an additional sixty (60) days.

F. Evaluation: During FY 2006, FDA will conduct a study to evaluate the costs and benefits of this program for both sponsors and the Agency.

X. FIRST CYCLE REVIEW PERFORMANCE PROPOSAL

A. Notification of Issues Identified during the Filing Review

1. Performance Goal: For original NDA/BLA applications and efficacy supplements, FDA will report substantive deficiencies identified in the initial filing review to the sponsor by letter, telephone conference, facsimile, secure e-mail, or other expedient means.
2. The timeline for such communication will be within 14 calendar days after the 60 day filing date.
3. If no deficiencies were noted, FDA will so notify the sponsor.
4. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.
5. FDA will provide the sponsor a notification of deficiencies prior to the goal date for 50% of applications in FY 2003, 70% in FY 2004, and 90% in FY 2005, FY2006, and FY 2007.

B. Good Review Management Principles Guidance: FDA will develop a joint CDER-CBER guidance on Good Review Management Principles (GRMPs), and publish final guidance by the end of FY 2003. The Good Review Management Principles will address, among other elements, the following:

1. The filing review process, including communication of issues identified during the filing review that may affect approval of the application.
2. Ongoing communication with the sponsor during the review process (in accordance with 21 CFR 314.102(a)), including emphasis on early communication of easily correctable deficiencies (21 CFR 314.102(b)).
3. Appropriate use of Information Request and Discipline Review letters, as well as other informal methods of communication (phone, fax, e-mail).
4. Anticipating/planning for a potential Advisory Committee meeting.
5. Completing the primary reviews – allowing time for secondary and tertiary reviews prior to the action goal date.
6. Labeling feedback – planning to provide labeling comments and scheduling time for teleconferences with the sponsor in advance of the action goal date

C. Training: FDA will develop and implement a program for training all review personnel, including current employees as well as future new hires, on the good review management principles.

D. Evaluation: FDA will retain an independent expert consultant to undertake a study to evaluate issues associated with the conduct of first cycle reviews.

1. The study will be designed to assess current performance and changes that occur after the guidance on GRMPs is published. The study will include collection of various types of tracking data regarding actions that occur during the first cycle review, both from an FDA and industry perspective (e.g., IR letters, DR letters, draft labeling comments from FDA to the sponsor, sponsor response to FDA requests for information).
2. The study will also include an assessment of the first cycle review history of all NDAs for NMEs and all BLAs during PDUFA 3. This assessment will include a more detailed evaluation of the events that occurred during the review process with a focus on identifying best practices by FDA and industry that facilitated the review process.
3. The study will also include an assessment of the effectiveness of the training program implemented by FDA.
4. FDA will develop a statement of work for the study and will provide the public an opportunity to review and comment on the statement of work before the study is implemented. The consultant will prepare annual reports of the findings of the study and a final study report at the end of the 5-year study period. The full (un-redacted)

study reports will be provided to the FDA Commissioner and a version of the study reports redacted to remove confidential commercial information or other information exempt from disclosure, will be made available to the public.

5. Development and implementation of the study of first cycle review performance will be a component of the Performance Management Plan conducted out of the Office of the Commissioner (see section X).
6. Administrative oversight of the study will rest in the Office of the Commissioner. The Office of the Commissioner will convene a joint CDER/CBER review panel on a quarterly basis as a mechanism for ongoing assessment of the application of Good Review Management Principles to actions taken on original NDA/BLA applications.

XI. IMPROVING FDA PERFORMANCE MANAGEMENT

A. Performance Fund: The Commissioner will use at least $7 million over five years of PDUFA III funds for initiatives targeted to improve the drug review process.

1. Funds would be made available by the Commissioner to the Centers based both on identified areas of greatest need for process improvements as well as on achievement of previously identified objectives.
2. Funds also could be used by the FDA Commissioner to diagnose why objectives are not being met, or to examine areas of concern.
3. The studies conducted under this initiative would be intended to foster:
   a. Development of programs to improve access to internal and external expertise
   b. Reviewer development programs, particularly as they relate to drug review processes,
   c. Advancing science and use of information management tools
   d. Improving both inter- and intra-Center consistency, efficiency, and effectiveness
   e. Improved reporting of management objectives
   f. Increased accountability for use of user fee revenues
   g. Focused investments on improvements in the process of drug review
   h. Improved communication between the FDA and industry
4. In deciding how to spend these funds, the Commissioner would take into consideration how to achieve greater harmonization of capabilities between CDER and CBER.

B. First Two Initiatives: Two specific initiatives will begin early in PDUFA III and supported from performance management initiative funds 1) evaluation of first cycle review performance, and 2) process review and analysis within the two centers.

1. First Cycle Review Performance
   See the First Cycle Review Performance (See section X. for details on this proposed study).
2. Process Review and Analysis
   a. In FY 2003, FDA will contract with an outside consultant to conduct a comprehensive process review and analysis within CDER and CBER. This review will involve a thorough analysis of information utilization, review management, and activity cost.
   b. The review is expected to take from 18-24 months, although its duration will depend on the type and amount of complexity of the issues uncovered during the review.
   c. The outcome of this review will be a thorough documentation of the process, a re-map of the process indicating where efficiencies can be gained, activity-based project accounting, optimal use of review tools, and a suggested path for implementing the recommendations.
   d. FDA would anticipate delivery of a report of the consultant's findings and recommendations in FY 2004-2005. The agency would consider these

recommendations in planning any redesign or process reengineering to enhance performance.

3. Further Studies

In subsequent years of PDUFA III, FDA may develop other study plans that will focus on further analysis of program design, performance features and costs, to identify potential avenues for further enhancement. Future studies would be likely to include a comprehensive re-analysis of program costs following the implementation of new PDUFA III review initiatives and the adoption of any process changes following the recommendations of the year 1 and 2 studies.

XII. ELECTRONIC APPLICATIONS AND SUBMISSIONS - GOALS

a. The Agency will centralize the accountability and funding for all PDUFA Information Technology initiatives/activities for CBER, CDER, ORA and OC under the leadership of the FDA CIO. The July 2001 HHS IT 5-year plan states that infrastructure consolidation across the department should be achieved, including standardization. The Agency CIO will be responsible for ensuring that all PDUFA III IT infrastructure and IT investments support the Agency's common IT goals, fit into a common computing environment, and follow good IT management practices.

b. The Agency CIO will chair quarterly briefings on PDUFA IT issues to periodically review and evaluate the progress of IT initiatives against project milestones, discuss alternatives when projects are not progressing, and review proposals for new initiatives. On an annual basis, an assessment will be conducted of progress against PDUFA III IT goals and, established program milestones, including appropriate changes to plans. A documented summary of the assessment will be drafted and forwarded to the Commissioner A version of the study report redacted to remove confidential commercial or security information, or other information exempt from disclosure, will be made available to the public. The project milestones, assessment and changes will be part of the annual PDUFA III IT report.

c. FDA will implement a common solution in CBER, CDER, ORA and OC for the secure exchange of content including secure e-mail, electronic signatures, and secure submission of, and access to application components.

d. FDA will deliver a single point of entry for the receipt and processing of all electronic submissions in a highly secure environment. This will support CBER, CDER, OC and ORA. The system should automate the current electronic submission processes such as checking the content of electronic submissions for completeness and electronically acknowledging submissions.

e. FDA will provide a specification format for the electronic submission of the Common Technical Document (e-CTD), and provide an electronic review system for this new format that will be used by CBER, CDER and ORA reviewers. Implementation should include training to ensure successful deployment. This project will serve as the foundation for automation of other types of electronic submissions. The review software will be made available to the public. .

f. Within the first 12 months, FDA will conduct an objective analysis and develop a plan for consolidation of PDUFA III IT infrastructure and desktop management services activities that will assess and prioritize the consolidation possibilities among CBER, CDER, ORA and OC to achieve technical efficiencies, target potential savings and realize cost efficiencies. Based upon the results of this analysis, to the extent appropriate, establish common IT infrastructure and architecture components according to specific milestones and dates. A documented summary of the analysis will be forwarded to the Commissioner. A version of the study report redacted to remove confidential commercial

or security information, or other information exempt from disclosure, will be made available to the public.

g. FDA will implement Capability Maturity Model (CMM) in CBER, CDER, ORA and OC for PDUFA IT infrastructure and investments, and include other industry best practices to ensure that PDUFA III IT products and projects are of high quality and produced with optimal efficiency and cost effectiveness. This includes development of project plans and schedules, goals, estimates of required resources, issues and risks/mitigation plans for each PDUFA III IT initiative.
h. Where common business needs exist, CBER, CDER, ORA and OC will use the same software applications, such as eCTD software, and COTS solutions.
i. Within six months of authorization, a PDUFA III IT 5-year plan will be developed. Progress will be measured against the milestones described in the plan.

XIII. ADDITIONAL PROCEDURES

A. Simplification of Action Letters

To simplify regulatory procedures, CBER and CDER intend to amend their regulations and processes to provide for the issuance of either an "approval" (AP) or a "complete response" (CR) action letter at the completion of a review cycle for a marketing application.

B. Timing of Sponsor Notification of Deficiencies in Applications

To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of an "information request" (IR) letter when each discipline has finished its initial review of its section of the pending application.

XIV. DEFINITIONS AND EXPLANATION OF TERMS

A. The term "review and act on" is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, 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.

B. A major amendment to an original application, efficacy supplement, or resubmission of any of these applications, submitted within three months of the goal date, extends the goal date by three months. A major amendment to a manufacturing supplement submitted within two months of the goal date extends the goal date by two months.

C. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.

D. Class 1 resubmitted applications are applications resubmitted after a complete response letter (or a not approvable or approvable letter) that include the following items only (or combinations of these items):

1. Final printed labeling

2. Draft labeling

3. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission)

4. Stability updates to support provisional or final dating periods

5. Commitments to perform Phase 4 studies, including proposals for such studies

6. Assay validation data

7. Final release testing on the last 1-2 lots used to support approval

8. A minor reanalysis of data previously submitted to the application (determined by the agency as fitting the Class 1 category)

9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category)

10. Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry.

E. Class 2 resubmissions are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

F. A Type A Meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting).

G. A Type B Meeting is a 1) pre-IND, 2) end of Phase 1 (for Subpart E or Subpart H or similar products) or end of Phase 2/pre-Phase 3, or 3) a pre- NDA/BLA meeting. Each requestor should usually only request 1 each of these Type B meetings for each potential application (NDA/BLA) (or combination of closely related products, i.e., same active ingredient but different dosage forms being developed concurrently).

H. A Type C Meeting is any other type of meeting.

I. The performance goals and procedures also apply to original applications and supplements for human drugs initially marketed on an over-the-counter (OTC) basis through an NDA or switched from prescription to OTC status through an NDA or supplement.