M B C

MASSACHUSETTS BIOTECHNOLOGY COUNCIL

Rec'd
8/13/98

August 4, 1998

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5600 Fishers Lane
Rockville, MD 20857

Docket No. 98N-0339

Dear Sir/Madame:

Pursuant to the letter dated July 23, 1998, from Dr. Zoon, CBER, requesting further public comments and dialogue on the implementation of the FDAMA, the Massachusetts Biotechnology Council (MBC) would like to submit the following for your review.

Enclosed is a copy of the final draft of the MBC's "Food and Drug Administration Modernization Act (FDAMA) of 1997, Recommendations for Implementation and Regulation" dated July 18, 1998, along with the MBC's "Comments for 'Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices,' Proposed Rule, 63 Fed. Reg. 31143 (June 8, 1998)", dated July 23, 1998.

We look forward to discussing these points at the August 14th public forum as well as directly. Thank you for your efforts regarding this matter.

Sincerely,

Janice Bourque
Executive Director

98D-0468

C5

245 First Street, 14th Floor, Cambridge, MA 02142 Tel 617/577-8198 Fax 617/577-7860 www.massbio.org

M B C

MASSACHUSETTS BIOTECHNOLOGY COUNCIL

July 18, 1998

Jane Axelrad
Associate Director for Policy
Food and Drug Administration
Office of Policy
5600 Fishers Lane, HFD-5
Rockville, MD 20857

98 JUL 30 A9:27 5114

Dear Ms. Axelrad:

The Massachusetts Biotechnology Council, Inc. (MBC) and its Member Companies have been meeting since February to define and analyze how the Food and Drug Administration Modernization Act of 1997 can be implemented in the most meaningful way.

The result of our deliberations is a White Paper, enclosed for your consideration, which has been also forwarded to the individuals listed below. Our Member Companies have worked diligently to draw from their experiences and to define what they need to accomplish the intent of FDAMA.

We hope that our recommendations, the product of thorough discussions, will be given serious consideration. We would appreciate the opportunity to meet with you to discuss the points addressed in the White Paper.

We look forward to hearing from you.

Yours truly,

Janice Bourque
Executive Director

cc: Michael Friedman, Acting Commissioner
William Schultz, Office of Policy
Dr. Janet Woodcock, CDER
Dr. Kathryn Zoon, CBER
John Marzelli, FDA Boston Office
Murray Lumpkin, CDER
Doug Sporn, CDER
Rebecca Devine, CBER
William Marnane, CVM
Robert Temple, CDER
Peggy Dotzel, Office of Policy
Minnie Baylor-Henry, CDER
Laurie Burke, CDER
Suzanne O'Shea, Ombudsmens Office

245 First Street, 14th Floor, Cambridge, MA 02142 Tel 617/577-8198 Fax 617/577-7860 www.massbio.org

M B C

MASSACHUSETTS BIOTECHNOLOGY COUNCIL

Food and Drug Administration Modernization Act (FDAMA) of 1997

Recommendations for Implementation and Regulation

Submitted by

Massachusetts Biotechnology Council, Inc.

July 18, 1998

Memorandum

DATE: July 18, 1998

TO: Dr. Michael A. Friedman, Acting Commissioner, FDA
William B. Schultz, Director, Office of Policy

CC: Jane Axelrad, Associate Director for Policy, Office of Policy
Dr. Janet Woodcock, Director, CDER
Dr. Kathryn Zoon, Director, CBER
John Marzelli, District Director, FDA Boston Office

Sections to be reviewed by the following additional FDA appointed individuals:

Tab 1-FDAMA §119 - Meetings & Performance Goals
Murray Lumpkin, CDER
Doug Sporn, CDER
Rebecca Devine, CBER

Tab 2-FDAMA §116 - Manufacturing Issues
Rebecca Devine, CBER
William Marnane, CVM

Tab 3-FDAMA §112 - Fast Track
Dr. Janet Woodcock, CDER
Rebecca Devine, CBER

Tab 4-FDAMA §§551(b)(3) & 551(a) - Off Label
Robert Temple, CDER
Peggy Dotzel, Office of Policy

Tab 5-FDAMA §114 - Pharmacoeconomics
Minnie Baylor-Henry, CDER
Laurie Burke, CDER

Tab A-FDAMA - Harmonization
Rebecca Devine, CBER

Tab B-FDAMA - Accountability
All Recipients

Tab C-FDAMA §404 - Ombudsmen's Role
Suzanne O'Shea, Office of Chief Mediator and Ombudsman

FROM: Massachusetts Biotechnology Council (MBC)

RE: Implementation of the Food and Drug Administration Modernization Act (FDAMA)

I. Statement of Intent

The Massachusetts Biotechnology Council, Inc. (MBC) submits this document to the Food and Drug Administration (FDA) with three objectives: (1) to identify issues that we believe are important and high priorities, (2) to commence a dialogue pursuant to the FDA's new mission of cooperation, and (3) to provide feedback to the FDA from industry to help the Agency as it formulates guidance documents and regulations pursuant to the enactment of the Food and Drug Administration Modernization Act (FDAMA). *See* FDAMA, § 406(b)(4), Pub. L. 105-115, 111 Stat. 2296 (Nov. 21, 1997). The MBC recognizes that this submission, while specific in its treatment of several issues, is general in places. Nevertheless, the MBC hopes that the document will begin a dialogue between our industry and the FDA, and that it will serve as the basis for ongoing discussion.

II. Background

The Massachusetts biotechnology industry consists of a community of approximately 200 mostly small companies. The research and development (R&D) initiatives of many of our Members are reaching the clinic, and several companies already have introduced breakthrough products into national and international health care markets.

The MBC recognizes that FDAMA is the embodiment of overwhelming bipartisan support for the safe and expeditious commercialization of innovative health care products. We are eager to assist the FDA in its FDAMA mission--to realize the "prompt approval of safe and effective new drugs and other therapies . . . so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease." 111 Stat. at 2298. As recognized by Congress, cooperation between the FDA and industry is essential to build the regulatory infrastructure necessary to achieve this mission. *See* FDAMA, § 406(b)(4).

III. Specific Issues

In the spirit of cooperation, representatives from several of the MBC's Member Companies formed a Working Group to collectively identify concerns with the FDA review and approval process and to propose improvements during FDAMA implementation. The Working Group has met over the past several months and identified specific priority issue areas: (1) performance goals, user fees, and meetings; (2) manufacturing issues; (3) fast track; (4) off-label uses; and (5) pharmacoeconomics. These areas became the focus for the work of subgroups, and their work product then was reviewed by the full Working Group and, ultimately, by other Member Companies and the MBC Board of Directors. The attached MBC work product is summarized in Figure 1.

Figure 1 FDAMA Implementation: MBC "Points to Consider" Submissions	
Tab 1	***Meetings and Performance Goals***, FDAMA, § 119: Points to consider for the development of policies, procedures, and guidelines for meetings between sponsors and the FDA under section 119 of the FDA Modernization Act of 1997 (FDAMA).
Tab 2	***Manufacturing Issues***, FDAMA, § 116: Points to consider for the development of policies, procedures and multicenter guidance documents related to manufacturing changes for drugs in the implementation of the FDA Modernization Act of 1997 (FDAMA). Proposed Regulation/Guidance: Changes to an Approved Application--Biological Products, Veterinary Drugs, and Human Drugs.
Tab 3	***Fast Track***, FDAMA, § 112: Points to consider for the development of policies, procedures and multicenter guidance documents related to the implementation of the "Fast Track Provisions" as described within the FDA Modernization Act of 1997 (FDAMA).
Tab 4	***Off-label***, FDAMA, §§ 551(b)(3), 553(a): Points to consider for the development of policies, procedures and multicenter guidance documents related to off-label information under the FDA Modernization Act of 1997 (FDAMA).
Tab 5	***Pharmacoeconomics***, FDAMA, § 114: Points to consider for the development of policies, procedures and multicenter guidance documents related to health care economic information under the FDA Modernization Act of 1997 (FDAMA).

IV. Overarching General Concerns

In addition to the specific proposals listed in Figure 1, the MBC Working Group identified three overarching concerns: (A) the importance of realizing consistency in handling specific applications both horizontally between the Center for Biologics Evaluation & Research (CBER) and Center for Drug Evaluation & Research (CDER), and vertically through the ranks of each Center, (B) the need for the FDA to operate in a transparent manner to increase its predictability and accountability, and (C) the importance of expanding and empowering the role of Chief Mediator and Ombudsman and the role of Ombudsman in each Center. The MBC's treatment of these issues are attached as listed in Figure 2.

Figure 2 FDAMA Implementation: MBC "General Concern" Submissions	
Tab A	Harmonization and Consistency in the Handling of Drugs and Biologics
Tab B	Increased Transparency and Accountability
Tab C	Cooperation between the FDA and Industry and Enhancement of the Roles of Industry Ombudsmen

V. PhRMA Submissions

The MBC has reviewed working drafts of several potential submissions by the Pharmaceutical Research and Manufacturers of America (PhRMA) to the FDA. The MBC generally supports the proposals it has reviewed. However, the MBC is submitting its own proposals to provide more detail in specific areas identified as priority areas by our Working Group.

VI. Request for FDA Action

The MBC recognizes that, through collaboration, the general public, FDA, and industry may realize the most fundamental objective of FDAMA-- the "prompt approval of safe and effective new drugs and other therapies . . . so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease." 111 Stat. at 2298. Our Working Group will continue to meet throughout the foreseeable future. The MBC urges the FDA to consider the concerns and suggestions identified herein and, as the FDAMA implementation process advances, to utilize the Working Group as a resource to respond to specific queries and to provide an industry perspective. In the spirit of cooperation mandated under FDAMA, the MBC invites the FDA to join in an ongoing dialogue to address the concerns raised above and those that will arise as the FDAMA implementation process advances. We look forward to the FDA's response.

POINTS TO CONSIDER

for

The development of policies, procedures, and guidelines for meetings between sponsors and the FDA under section 119 of the FDA Modernization Act of 1997 (FDAMA)

June, 1998

Prepared by:
Massachusetts Biotechnology Council (MBC)

FDA Modernization Act (FDAMA)
§119: Meetings
Points to Consider

Introduction

FDAMA has provided a guideline for the management of meetings between sponsors and FDA. The purpose of these meetings should be to reach agreements on the design and size of clinical trials and preclinical studies, and to resolve any issues regarding product manufacturing and testing. Guidance should be provided to FDA reviewers to maintain an appropriate level of consistency between FDA reviewing divisions.

The Massachusetts Biotechnology Council (MBC) is aware that industry and FDA engaged in extensive discussions about meetings during the Prescription Drug User Fee Act (PDUFA) and PDUFA-2 (together "PDUFA") negotiations, and that agreements were reached. Nevertheless, we propose these additions/clarifications to the provisions of FDAMA. Although our suggestions may exceed PDUFA agreements in some instances, we believe that this Points to Consider document reflects the resource commitment from the FDA that our industry needs to make breakthrough products available to patients in a time-sensitive manner and to otherwise fulfill FDAMA objectives.

I. Setting up Meetings:

The MBC proposes that, in accordance with the provisions of PDUFA, FDAMA and related negotiations and agreements, meetings be set up in the following manner:

A. Regardless of whether the proposed meeting is a conference call or an in-person meeting, the sponsor shall request a formal meeting in writing. These written requests shall include specified objectives, requested FDA attendees, a tentative agenda, and a suggested length for the meeting.

B. FDA shall agree to the objectives/agenda in writing within 14 days of the request, and FDA shall determine the meeting type (A,* B** or C***), the length of the meeting, and the required FDA attendees, and FDA shall schedule the meeting to take place within 30, 60, or 75 days (for meeting types A, B, and C, respectively) from receipt of the sponsor's request.

C. The sponsor shall provide the meeting package and final agenda to FDA within 2 weeks (for type A or C meetings) or 4 weeks (for type B meetings) of the scheduled meeting.

In addition, the MBC proposes that meetings for products designated fast track products always take place within 30 days from receipt of the sponsor's request. Within 14 days of the sponsor's request, FDA shall schedule these meetings accordingly. This time-frame is

---

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

** Type B meeting: A (1) pre-IND, (2) end of Phase 2, (3) end of Phase 1 for Fast Track (Subpart E, Subpart H, or similar products), or (4) a pre-NDA/BLA/PLA meeting.

*** Type C meeting: Any other type of meeting.

consistent with other efforts to accelerate the approval of fast track products and recognition of the importance of this objective under FDAMA.

II. Holding Meetings:

The MBC suggests that, in accordance with the provisions of PDUFA and related negotiations and agreements, meetings be held in the following manner:

A. The sponsor shall manage the timing of meetings requested by the sponsor in a manner that will address the sponsor's objectives.

B. The sponsor and FDA shall summarize agreements at the end of the meeting.

III. Meeting Minutes:

The MBC proposes that the following procedures govern meeting minutes:

A. As required pursuant to the PDUFA letter agreement (from Donna E. Shalala, Secretary of Health and Human Services, to Hon. Thomas J. Bliley, Jr., Committee on Commerce, House of Representatives, dated November 12, 1997), FDA shall prepare meeting minutes and provide them to the sponsor within 30 days of the meeting.

B. If FDA fails to prepare meeting minutes or fails to provide them to the sponsor within 30 days, the sponsor shall have the option to submit its own meeting minutes to the FDA. Absent objection from the FDA within 10 days of receipt of such a submission, the sponsor's submission shall become the official meeting minutes.

C. The sponsor shall be given an opportunity to provide corrections to the minutes. The sponsor shall provide such corrections within 15 days of receiving the minutes from the FDA. The FDA then shall respond to the corrections submitted by the sponsor within 15 days. If this process results in disagreements, the sponsor may appeal any dispute, and the FDA shall render a decision within 30 calendar days.

IV. Type of Meetings:

To realize the objectives of FDAMA and PDUFA-2, the MBC believes that:

A. More than 1 type B meeting for each pre-IND, end-phase 2, end-phase 1 for fast-track, and pre-BLA/PLA/NDA meeting shall be allowed in the case of major changes to clinical design, or other major changes in clinical, preclinical, or product development.

B. Interactions with FDA shall not be strictly formal, and informal communications shall not be limited as a result of formal meeting opportunities and requirements.

V. Performance Goals:

FDAMA has provided performance goals for review times of initial marketing applications and efficacy and manufacturing supplements. For example, 90% of all standard NDA/PLA/BLAs and efficacy supplements will be acted on, i.e. an action letter will be issued within 12 months of receipt in fiscal year 1998, and 90% of these will be acted on within 10 months by fiscal year 2002.

The MBC proposes that, for the same reasons that fast-track products are prioritized generally, fast-track products must be designated categorically to meet the highest performance goals during the period of phase-in.

In addition, for all product applications, it is critical for the sponsor to know if FDA has questions/concerns during the review process to allow time to respond to these questions prior to the due date of the action letter. MBC would like to have a mechanism in place for companies to get a status of the review from FDA well in advance of the action date.

Accordingly, MBC proposes the following:

A. The reviewer shall provide a status of the review to the sponsor during early stages of review of the original application for a resubmitted application, and provide monthly updates, as applicable.

B. For the review time exceeding the target action time**** (falling outside of 90% for FY 1998, 90% for FY 1999, and 50% for FY 2000), the best effort shall be put forth by the Agency to keep the review time close to the target time. This can include any additional communication and meetings between the Agency and the sponsor to discuss issues causing the delay of the review.

C. For fast-track reviews, a sponsor may submit portions of an application for the approval of the product before the sponsor submits a complete application. FDAMA, 111 Stat. 2310 (*to be codified at* 21 USC § 356 (c)(1)). Deficiencies in these submissions shall be made clear to sponsors on an ongoing basis and in as timely a manner as possible to promote the policy of accelerating the review of fast track products.

**** Action time is defined as the time from receipt of the submission to the time an action letter is issued by FDA. Target action time is the current year's target for action time.

POINTS TO CONSIDER

for

The development of policies, procedures and multicenter guidance documents related to manufacturing changes under the FDA Modernization Act of 1997 (FDAMA)

June 1998

Prepared by
Massachusetts Biotechnology Council (MBC)

FDA Modernization Act (FDAMA)
§116: Manufacturing Changes

Introduction

The MBC's Working Group has engaged in extensive discussions of the manufacturing changes associated with FDAMA. This document, a summary of many of the concerns and issues identified by the Group, is accompanied by another MBC submission, entitled "Proposed Guidance: Changes to an Approved Application: Biological Products, Veterinary Drugs, and Human Drugs."

The MBC's Proposed Guidance embodies existing FDA guidance, but with modifications inspired by FDAMA and the shared experience of our industry. The MBC used the FDA's Guidance for Industry, Changes to an Approved Application: Biological Products (Center for Biologics Evaluation and Research, CBER) (July 1997) and Guidance for Industry, Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (CBER and Center for Drug Evaluation and Research, CDER) (July 1997) as models for its Proposed Guidance. Therefore, for the purposes of interpretation, the MBC's Proposed Guidance should be construed to be consistent with these FDA guidances.

Background Information

Historically, manufacturing changes for drugs (CDER regulated) have been subjected to a three-tier approach. These changes have been deemed: (1) to need pre-approval from FDA; (2) to be permissible prior to FDA approval; or (3) to be acceptable contingent upon a sufficient description in the annual report. More recent guidance documents--Scale-Up and Post Approval Changes (SUPAC)--have addressed levels of change that may be made in the components or composition of the drug, site of manufacture, scale-up/scale-down of manufacture and manufacturing process and equipment for certain specified types of products. It is expected that the practice of issuing guidance documents that address post-approval change procedures for specific classes of Drugs, Biologics, and Veterinary Drugs, Bulk Chemicals, and so forth will continue.

FDA's practice has been to require preapproval for all manufacturing changes for biologics (CBER regulated). However, CBER has published a Final Rule (62 Fed. Reg. 39890), and, with CDER, a Final Guidance document (62 Fed. Reg. 39904) that require applicants to report changes by one of three mechanisms. The potential for the manufacturing change to have an adverse effect on the "identity, strength, quality, purity, or potency of the product as they may related to the safety or effectiveness of the product" controls which mechanism is appropriate.

The new law (which adds section 506A to the Food, Drug and Cosmetic Act) applies to manufacturing changes made with regard to a drug (section 501), an animal drug (section 512), or a biological (section 351 of the Public Health and Service Act). When no specific Guidance Document already exists (e.g., SUPAC), this procedure provides guidance to allow a change to be made and a product made with the change to be distributed. However, before distributing the product, the holder of the approved application or license must validate the effects of the change on the identity, strength, quality, purity, and potency as they relate to the safety or effectiveness of the drug. In addition to such validation, the

provision requires additional action depending on whether the change constitutes a major manufacturing change.

Major manufacturing changes must be submitted to FDA in a supplemental application, and they require FDA preapproval prior to distribution. Changes qualifying as major changes are those that have substantial potential to adversely affect the "identity, strength, quality, purity or potency of the product as they may relate to the safety or effectiveness of the product." Examples include:

- a change in the qualitative or quantitative formulation of the drug, or
- a change determined by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence, or
- a change determined by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug.

Changes that are NOT major manufacturing changes ("other manufacturing changes") shall, as determined by the Secretary, be classified by one of the two following ways:

- Changes that may be made at any time without submission of a supplement and then reported annually, along with supporting data, or
- Changes that are required to be reported in a supplement.

If a supplement is required, the drug may be distributed 30 days after the application is received unless, within the 30-day period, the applicant is notified that prior approval is required. In the event that a supplemental application is not approved by the FDA, the FDA is authorized to order that distribution of any product made with the change cease.

Overall, the new law essentially codifies FDA's earlier guidance to distinguish between major and minor manufacturing changes and, with respect to biologicals, is consistent with the decision to eliminate the separate establishment license application.

Issues related to Implementation of this Section

1) Implementation by Guidance or Regulation?

As currently stated, the law gives the FDA the option to categorize different types of manufacturing changes either by regulation or guidance. This new provision will be implemented by regulations within 24 months of the date of the Act (but may or may not categorize types of manufacturing changes depending on whether FDA utilizes the guidance option for that process).

There is concern in the life science sector that this process will take up to two years, and the process to classify changes has not been specified. The MBC recognizes that FDA needs to maintain some flexibility in categorization of manufacturing changes. Nevertheless, we recommend that FDA propose a harmonized guideline implementing manufacturing changes which include categorization of most manufacturing changes. We recommend that these guidelines be based upon the most recent guidance documents that encompass the spirit of FDAMA, and that they embody recognition that manufacturing processes and

facilities used to produce a product will continue to undergo refinement or scale-up which, in many cases, will result in innovations beneficial to consumers. Failure to specifically address the process of categorization in detail could significantly restrict consumer benefit.

2) **Uniformity of Change Classifications**

Currently, due to the evolution of the manufacturing change classifications in CBER, CDER, and CVM, guidance documents, draft guidance documents, or regulations differ in their classification and notification schemes. The experience of several MBC members is that the FDA staff do not consistently use the most up-to-date documents. Given a two-year limit for the FDA to implement new guidance documents or regulations, there is a significant concern about how changes will be addressed by the Centers and Field Offices during this period of implementation.

Especially in light of the intent of FDAMA to standardize these classifications and to implement changes in a timely manner, we in the life science industry recommend that all FDA Centers and Field Offices follow the most recent guidance documents during the < 2-year period prior to implementation of the new guidance. This approach should implement a standard program of change control that encompasses the spirit of FDAMA and that recognizes that manufacturing processes and facilities used to produce the product will continue to undergo refinement or scale-up, which in many cases will result in innovations beneficial to consumers. Applicants should remain responsible for validating these changes and providing sufficient notice to the FDA.

Proposed Guidance

Changes to an Approved Application: Biological Products, Veterinary Drugs, and Human Drugs

June 1998

Prepared by:
Massachusetts Biotechnology Council (MBC)

Preliminary Statement

The life science sector has proposed that changes to all approved or licensed products (biologicals, veterinary and human drugs) be regulated uniformly, meaning that the Agency adopt homogenous criteria for reporting changes to the FDA regarding the product, production process, quality controls, equipment, and facilities. This Proposed Guidance constitutes a preliminary statement and collection of recommendations, which the MBC is submitting to commence what we hope will become an ongoing dialogue between our industry and the FDA.

The MBC's Proposed Guidance embodies existing FDA regulations and guidances, but with modifications, including the elimination of some requirements, inspired by FDAMA and the shared experience of our industry. For the purpose of interpretation, the MBC intends, therefore, that its Proposed Guidance be construed as a document modeled upon the FDA's Guidance for Industry, Changes to an Approved Application: Biological Products (Center for Biologics Evaluation and Research, CBER) (July 1997), and Guidance for Industry, Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (CBER and Center for Drug Evaluation and Research, CDER) (July 1997).

Proposed Guidance

I. Introduction

Frequently, a sponsor determines that it is appropriate to make a change in the product, labeling, production process, quality controls, equipment, facilities, or responsible personnel established for that product pursuant to its approved license application. The current requirements for reporting such changes to the FDA for licensed biological products, veterinary drugs, and human drugs are set forth under sections 601.12, 514.8, and 314.70 of Title 21 of the Code of Federal Regulations.

This Guidance is intended to assist manufacturers in determining which reporting mechanism is appropriate for a change to an approved license, new drug, or new veterinary drug application. Some existing Guidance Documents (e.g. Scale-Up and Post-Approval Changes, SUPAC) provide specific guidance for changes of certain classes of products. In addition to the applicable regulations regarding any change to a licensed product or biological, an applicant making a change must conform to other applicable law and regulations including the current good manufacturing practice (cGMP) requirements of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 351 (a) (2)(B)) and applicable regulations in 21 CFR parts 210, 211, 600-680, and 820. For example, manufacturers must comply with record keeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection

Under each subsection of this guidance, FDA describes a category of changes to be reported. FDA also provides a list of various changes that the Agency believes currently fall under each category. A separate section on labeling describes the labeling changes that must be submitted as supplements that require prior approval, supplements that must be submitted at the time that a change is made, and supplements that may be submitted in an annual report

II. Reporting Requirements

Changes must be reported to FDA via: (1) a supplement that requires approval prior to distribution, (2) a supplement that must be submitted to FDA at least 30 days prior to distribution of the product made using the change, or (3) an annual report. The method of reporting required depends upon the potential for the change to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors relate to the safety and effectiveness of the product. The three reporting categories for changes to an approved application, which correlate with the requirements identified in 1-3, are:

1. *Preapproval Supplement*:: Changes that carry substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

2. *Supplement with Notice*:: Changes that carry moderate potential to adversely effect the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

3. *Notice in Annual Report*:: Changes that carry minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

In all cases, before distributing a product made using a change, the applicant/sponsor must demonstrate through appropriate validation and/or other clinical and non-clinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as these factors may impact the safety or effectiveness of the product.

Changes to a product package label, container label, and package insert require either: (1) submission of a supplement with FDA approval needed prior to product distribution; (2) submission of a supplement with product distribution allowed at the time of submission of the supplement; or (3) submission of the final printed label in an annual report. Changes to advertising and promotional labeling must be made in accordance with the provisions of 21 CFR 314.81 or 21 CFR 510.300. These regulations require the submission to FDA of specimens of mailing pieces and any other labeling or advertising devised for promotion of a drug product/veterinary drug product at the time of initial dissemination of the labeling, and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except that the sample of the drug product may be omitted from the container

A. Changes requiring submission and approval of a supplement prior to distribution of the product made using the change (major changes).

Changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement and approval by FDA before a product made using the change is distributed. For a change under this category, an applicant is required to submit a supplement to the approved license application that includes: (1) a detailed description of the proposed change; (2) the product(s) involved; (3) the manufacturing site(s) or area(s) affected; (4) a description of the methods used and

studies performed to evaluate the effect of the change on the product's identity, strength, quality, purity, and potency of the product as they may relate to its safety or effectiveness; (5) a summary of the data derived from those studies; (6) relevant validation protocols and summary data; and (7) a reference list of relevant standard operating procedures (SOPs). As noted, the applicant must obtain approval of the supplement by FDA prior to distribution of the product made using the change.

In FDA's experience, the following changes to a product, production process, quality controls, equipment, facilities, or responsible personnel have caused detrimental effects on the identity, strength, quality, purity, or potency of products as they related to the safety or effectiveness of the product even where applicants performed validation or other studies. FDA believes that these changes would generally have a substantial potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness and that the Agency's continued premarket review and approval of such changes is currently necessary to protect the public from products whose identity, strength, quality, purity, potency, safety, or effectiveness may be compromised:

1. Process changes including, but not limited to:

   - A new or revised purification process, including a change in a column;
   - A change in the chemistry or formulation of solutions used in processing;
   - A change in the sequence of processing steps or addition, deletion, or substitution of a process step; or
   - Reprocessing of a product without a previously approved reprocessing protocol.

2. Any change in manufacturing processes or analytical methods that:

   - Results in change(s) of specification limits or modification(s) in potency, sensitivity, specificity, or purity;
   - Establishes a new analytical method;
   - Deletes a specification or an analytical method;
   - Eliminates tests from the stability protocol; or
   - Alters the acceptance criteria of the stability protocol.

3. Scale-up requiring larger processing or purification equipment (applies to production up to the final purified bulk).

4. A change in the composition or dosage form of the product or ancillary components (e.g., new or different excipients, carriers, or buffers).

5. A new lot of, new source for, or different, in-house reference standard or reference panel (panel member) resulting in modification of reference specifications or an alternative test method.

6. Extension of the expiration dating period and/or a change in storage temperature, container/closure composition, or other conditions, other than changes based on real time data in accordance with a stability protocol in the approved license application.

7. Change of the site(s) at which manufacturing, other than testing, is performed; addition of a new location (including donor centers manufacturing platelets and/or performing automated pheresis procedures); or contracting of a manufacturing step in the approved license, to be performed at a separate facility.

8. Conversion of production and related area(s) from single to multiple product manufacturing area(s). (The addition of products to a multiple product manufacturing area could be submitted as an "Annual Report" if there are no changes to the approved and validated cleaning and changeover procedures and no additional containment requirements.)

9. Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions.

B. Changes requiring submission of a supplement at least 30 days prior to distribution of the product made using the change.

Changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement to FDA at least 30 days prior to distribution of a product made using the change. The requirements for the content of these supplements are the same as for those requiring approval prior to distribution.

Some examples of changes to the product, production process, quality controls, equipment, and facilities that FDA currently considers to have moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are set forth in the following list, which FDA has developed based on experience gained in reviewing submissions received in the past.

1. Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.

2. Addition or reduction in number of pieces of equipment (e.g., centrifuges, filtration devices, blending vessels, columns, etc.) to achieve a change in purification scale not associated with a process change.

3. Change in the site of testing from one facility to another (e.g., from a contract lab to the license holder; from an existing contract lab to a new contract lab; from the license holder to a new contract lab).

4. Change in the structure of a legal entity that would require issuance of new license(s), or change in the name of the legal entity or location that would require reissuance of license(s).

5. Downgrade of a room or area environmental quality classification except for aseptic processing areas.

In certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may

determine that the product made using the change may be distributed at the time the FDA receives the supplement. The following are changes that in FDA's experience have been submitted properly with the appropriate information, and could be implemented at the time of receipt of the supplement by FDA without a previously approved comparability protocol.

1. Addition of release tests and/or specifications or tightening of specifications for intermediates.

2. Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product.

In addition, applicants that use a comparability protocol to validate a proposed change may request that a change usually subject to supplement submission and approval prior to distribution be reported as a change subject to supplement submission at least 30 days prior to distribution of the product made using the change, or as a "Changes Being Effected" supplement submission, in which event the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

C. Changes to be described in an annual report (minor changes).

Changes to the product, production process, quality controls, equipment, facilities, or responsible personnel that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are required to be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the application. For changes under this category, the applicant is required to submit a list of all products involved in the annual report; and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, a cross-reference to relevant validation protocol(s) and/or SOPs, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

Some examples of changes that FDA currently considers to have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are listed below. The list, which is not all-inclusive, contains items that, in FDA's experience reviewing supplements, have caused few instances in which an adverse effect on the product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness has been observed.

1. Modification of an approved manufacturing facility or room(s) that is not likely to have an adverse effect on safety, sterility assurance, purity, or potency of product;

2. Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures and there are no additional containment requirements.

3. Increase in aseptic manufacturing scale for finished product without a change in equipment (i.e. increased number of vials filled (< 10 X).

4. Modifications in analytical procedures with no change in the basic test methodology or existing release specifications, provided the change is supported by validation data.

5. Change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale.

6. Establishment of a new working cell bank derived from a previously approved master cell bank according to a SOP on file in the approved application.

7. Replacement of an in-house reference standard or reference panel (or panel member) according to SOPs and specifications in an approved license application.

8. Tightening of specifications for existing reference standards to provide greater assurance of product purity, identity, and potency.

9. Establishment of an alternate test method for reference standards, release panels, or product intermediates, except for release testing of intermediates licensed for further manufacture.

10. Change in the storage conditions of in-process intermediates based on data from a stability protocol in an approved application, which does not affect labeling, except for changes in storage conditions which are specified by regulation.

11. Change in shipping conditions (e.g., temperature, packaging, or custody) based on data derived from studies following a protocol in the approved license application (except for changes in shipping conditions that are required by regulation to be submitted as a supplement.

12. Change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications).

13. Addition of time points to the stability protocol.

III. Comparability Protocols

A comparability protocol is a supplement that establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the safety and effectiveness of a product. A new comparability protocol, or a change to an existing one, requires approval prior to implementation because it may result in decreased reporting requirements for the changes covered. In general, a decrease in the reporting requirement will be one reporting tier, e.g., from supplement with distribution of product in 30 days to an annual report, or from prior approval supplement to supplement with distribution of product in 30 days. In some cases the decrease may be greater. The reporting category will be established at the time that the comparability protocol is approved. FDA will review and approve generic comparability protocols for all relevant product classes to be used by any sponsor.

IV. Labeling Changes

Changes to labeling are required to be submitted to the FDA in one of the following ways:

1. As a supplement requiring FDA approval prior to distribution of a product with the labeling change;

2. As a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval; or

3. In an annual report.

Some examples of changes to labeling that FDA currently considers to be appropriate for submission in each of these three categories are listed below. These lists are not intended to be comprehensive. Promotional labeling and advertising must be submitted to FDA at the time of initial dissemination or publication.

A. Labeling changes requiring supplement submission - FDA approval must be obtained before distribution of the product with the labeling change.

Any proposed change in the package insert, package label, or container label, except those described in the following sections is required to be submitted as a supplement and receive FDA approval prior to distributing a product with the label change. In such a supplement, the applicant is required to present clearly the proposed change in the label and the information necessary to support the proposed change. The following list contains some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.

2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.

3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another product.

7. Change in container labels for licensed blood.

B. Labeling changes requiring supplement submission - product with a labeling change may be distributed before FDA approval.

A supplement is required to be submitted for any change to a package insert, package label, or container label that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safety of the use of the product; or deletes false, misleading, or unsupported indications for use or claims for effectiveness. The applicant may distribute a product with a label bearing such a change at the time the supplement is submitted, although the supplement is still subject to approval by FDA. The following list includes some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Addition of an adverse event due to information reported to applicant or FDA.

2. Addition of a precaution arising out of a post-marketing study.

3. Clarification of the administration statement to ensure proper administration of the product.

C. Labeling changes requiring submission in an annual report.

A package insert, package label, or container label with editorial or similar minor changes or with a change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form must be described in an annual report. Some examples that are currently considered by FDA to fall into this reporting category include:

1. Changes in the layout of the package or container label without a change in content of the labeling.

2. Editorial changes such as adding a distributor's name.

3. Foreign language versions of the labeling if no change is made to the content of the approved labeling and a certified translation is included.

POINTS TO CONSIDER

for

The development of policies, procedures and multicenter guidance documents related to the implementation of the "Fast Track Provisions" as described within the FDA Modernization Act of 1997 (FDAMA)

June, 1998

Prepared by:
Massachusetts Biotechnology Council (MBC)

FDA Modernization Act (FDAMA)
§112: Fast Track Drugs and Biologics
Points to Consider

Introduction

Section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) requires FDA to establish a new program, known as the "fast track program," to expedite the development and approval of important new drugs and biological products. This provision codifies and expands upon FDA's successful efforts in the mid-1990s to speed patient access to new AIDS drugs, so that patients with other serious diseases may also receive early access to breakthrough products.

FDAMA requires FDA to grant "fast track designation" to sponsors whose products are intended for the treatment of serious or life-threatening conditions and for which the sponsor demonstrates a potential to address unmet medical needs. Designation may be sought when Phase I clinical trials are initiated, or any time thereafter.

Fast track designation is intended to "flag" products that represent potential therapeutic breakthroughs early in the clinical development process, so that FDA staff can provide appropriate priority to such products. In effect, for all important new products, fast track designation codifies the special attention that AIDS drugs were accorded simply for being AIDS drugs. It also provides a mechanism for the Agency to recognize the priority nature of such drugs long before the NDA or BLA is filed.[1]

In this paper, the MBC has identified changes that our industry believes are necessary to maximize our opportunity under FDAMA to serve patients through the development and introduction of breakhrough products for serious or life-threatening conditions. We hope and expect that close collaboration between fast track products sponsors and your Agency will occur throughout product development and evaluation. While FDAMA formalizes (and, in some cases, modifies) certain regulations and best practices, we believe that the spirit of the fast track provision--as well as the general exhortation contained in subsection (a)(1)--should be reflected in all interactions between sponsors and FDA.

Given the priority nature of fast track products, we urge you to ensure that fast track products stand first-in-line with respect to new PDUFA-2 performance goals, which will be phased in over the next few years. For example, the new performance goal for protocol agreements, under which sponsors may seek and obtain concurrence on the adequacy of proposed clinical trial protocols to meet proposed indication labeling, is scheduled to apply to 60% of all NDAs/BLAs in FY99, and increasing percentages of applications in subsequent years. We believe that the spirit of the fast track provision strongly suggests that FDA should ensure that it has allocated sufficient resources for all fast track product sponsors who wish to enter into such agreements before it allocates resources to non-fast track product sponsors.

Indeed, we encourage you to adopt a general principle that all PDUFA-2 performance goals should be applied to fast track products during the first year for which a performance goal is established, even if that goal (i.e., 90% performance) is not fully implemented for several years. Thus, implementation of a 60% performance goal in FY99 should consist of 90% performance for fast track products and the percentage of non-fast track products necessary to meet the overall goal. We also encourage the Agency to

[1] Under PDUFA-1, products were not classified "priority" or "standard" until a NDA or BLA was filed.

track products necessary to meet the overall goal. We also encourage the Agency to document the implementation of this approach through the tracking and reporting mechanism that you are developing for new performance goals.

We further suggest that the nature of fast track products justifies exceeding performance goals to the extent resources permit. For example, FDA should make reasonable attempts to accommodate a fast track product sponsor's request for a Type A meeting in less than the 30-day deadline and a Type B meeting faster than the 60-day goal. We particularly urge you to resolve procedural and scientific disputes that concern fast track products faster than the performance goals established under PDUFA-2.

Generally, guidelines and/or procedures developed by your Agency that pertain to the implementation of the fast track provisions of the Act should provide a framework that defines the process, while allowing flexibility to enable FDA and the sponsor to work out a drug development program on a case-by-case basis. The MBC recognizes and supports in principle the prototype guidance document on fast track products developed by the Pharmaceutical Research and Manufacturers of America (PhRMA).[2]

The MBC offers the following comments and suggestions to be considered and addressed in the development of policies, procedures and guidance documents related to the implementation of the "Fast Track Provisions" as described within the FDA Modernization Act of 1997 (FDAMA).

Definitions and Scope

The following are our suggestions for defining certain terms that are used, but not defined, in FDAMA:

• Serious and life-threatening conditions: The preamble contained in the Notice of Proposed Rulemaking for accelerated approval (June 1992) discussed how FDA intended the concept of "serious and life-threatening conditions" to apply under the accelerated approval regulation. This discussion provided for a broad and flexible application of this concept and cited a variety of examples of conditions which are considered serious or life-threatening. Unfortunately, not all CDER/CBER divisions have accepted or implemented this broad approach. Some companies have been informed by certain divisions that only AIDS and cancer are "serious" enough to be eligible for accelerated approval. For this reason, the House Report[3] on FDAMA reiterated the approach contained in FDA's June 1992 *Federal Register* notice. (See Appendix A.) We urge you to ensure that this approach is implemented in a consistent manner be all reviewing divisions.

• Demonstrated potential to address unmet medical needs: We believe a similarly broad approach should be applied to the concept of "unmet medical needs." If there is no FDA-approved treatment for a disease, there is obviously an unmet medical need for the first such treatment. But unmet medical needs also exist for the many diseases for which imperfect treatments exist. In general, we believe that any product that demonstrates the potential to introduce significantly greater safety and/or efficacy than existing products should be recognized as meeting unmet medical needs. The

[2] The PhRMA fast track guidance document was submitted to the Food and Drug Administration for consideration on 31 March 1998.

[3] H. Rep. No. 105-310, at 55-56 (1997).

following examples are representative (but should not be considered a comprehensive listing of all such cases):

- Existing treatment(s) is effective in some, but not all, patients, and the new treatment shows potential for efficacy in other patients;
- Existing treatment(s) offers temporary clinical benefits, and the new treatment shows potential for longer-term benefit;
- Existing treatment(s) alleviates symptoms but does not address the underlying pathology, and the new treatment shows potential to address the underlying disease;
- Existing treatment(s) has significant risks or side effects, and the new treatment is potentially safer or better tolerated;
- Existing treatment(s) consists of a product derived from human or animal sources (for which viral transmission is an unavoidable risk), and the new treatment consists of a recombinant version of the existing product; and
- Existing treatment(s) require injection, infusion, or surgery, and the new treatment is less invasive.

Since a product cannot be *proven* to meet an unmet medical need until after the completion of one or more pivotal clinical trials, the legislation provides that products that merely demonstrate the "potential" to do so are eligible for fast track designation. The requirement for demonstration of such potential should automatically be considered to have been met whenever a product would constitute an entirely new therapeutic approach to a disease or has a different mode of action than existing therapies. Modest proof of concept (i.e., in vitro or animal studies) should be required in such cases. On the other hand, new treatments which are chemically similar to existing treatments should be subjected to greater proof-of-concept requirements to prevent therapeutically equivalent products from receiving fast track designation.

• Surrogate endpoints - The fast track program codifies FDA's policy of granting accelerated approval to products that have been demonstrated to have an effect on an unvalidated surrogate endpoint that is reasonably likely to predict clinical benefit and subjecting such approvals to certain postapproval requirements.[4] The postapproval requirements specified in subsection (b)(2) should similarly apply to fast track products approved on this basis.

However, fast track products that are approved on the basis of their effect on either a clinical endpoint or a validated clinical endpoint should continue to receive a regular approval that is not subject to these postapproval requirements. Sponsors of such products may wish to participate in the fast track program in order to obtain rolling review or other fast track program benefits. We support the two-track program proposed by PhRMA, which is designed to ensure that sponsors of clinical endpoint products can obtain fast track program benefits without sacrificing the benefits of a regular approval.

Finally, we note that FDAMA requires the Secretary to establish a program to encourage the development of appropriate surrogate endpoints. We suggest that this program consist of quarterly conferences at which industry-proposed surrogate endpoints can be introduced and discussed. We believe that special attention should be paid to two categories of surrogate endpoints: (1) those that could be used for any chronic and degenerative disease for which demonstration of clinical benefit would

[4] 21 CFR § 312.80, § 314.500 and § 601.40.

otherwise require a significantly longer or larger clinical trial; and (2) those that could have broad applicability to a class of technologies that is being studied in various indications, such as gene or cell therapies.

Fast Track Product Designation Process

As described in FDAMA, a request for the designation as a fast track product may be made concurrently with, or at any time after, submission of an application for the investigation of the drug (IND). Therefore, a fast track product designation could become effective as early as the phase I clinical trial stage. The drug or biologic would be recognized and treated as a fast track product throughout the remainder of the drug development and approval process. Once the designation is granted, we believe that such designation should only be withdrawn in two circumstances. First, FDA may withdraw designation at any time after designation has been granted if the sponsor demonstrates, through its pivotal clinical trial design, that it is no longer pursuing an indication for a serious or life-threatening disease. Second, FDA may withdraw designation if, following both an advisory panel meeting and a complete review of the NDA/BLA, it determines that the drug does not meet an unmet medical need. In either case, we urge that designation be withdrawn only after notice to the sponsor and the opportunity for an informal hearing.

We propose that fast track designations be issued by the Director of the reviewing Division, but also in a manner that ensures consistency across divisions. Designation requests should include adequate documentation that the drug meets the two criteria for fast track designation (i.e., intended to treat a serious or life-threatening condition and demonstrates potential to address unmet medical needs).

Sponsors should specify whether or not they expect to seek approval on the basis of unvalidated surrogate endpoints under the new statutory standard for approval (and with the postapproval requirements) contained in subsection (b), either in their designation request or as soon as is feasible thereafter, to facilitate early cooperation and collaboration in the identification of appropriate surrogate endpoints. It is to the advantage of both the sponsor and FDA to discuss the proposed clinical pathway as early as possible in the drug development process, particularly when the sponsor anticipates using new and unvalidated surrogate endpoints. However, for the reasons described earlier, designation should not be limited to products for which unvalidated surrogate endpoint studies are intended.

If an IND has not been submitted for the product, the sponsor may request the fast track designation when submitting the IND. In a case where an IND has already been submitted, the sponsor may submit a request for the fast track designation that incorporates the IND submission (and, if appropriate, any orphan drug designation request) by reference, with supplemental information only as necessary to explain why the sponsor believes that the product meets the statutory criteria. Reviewing divisions should grant or deny designation, in writing, within 60 days of receipt of the sponsor's request, and FDA should include divisional statistics about the number of requests received, granted, and denied, as well as whether the 60-day deadline is being consistently met, in the annual reports to Congress that are required elsewhere in FDAMA.

In the absence of a sponsor's petition, the reviewing division Director may on his/her own initiative, make the determination, after the NDA is submitted that a new drug or biological product is eligible for inclusion in the fast track system.

IND Process

Once the decision has been made to grant fast track designation, the mutual objective of FDA and the sponsor should be to demonstrate, as rapidly as possible, whether the product is safe and effective and the adequacy of manufacturing controls.

In addition to the standard meetings (i.e., pre-IND, end of phase 2, and pre-NDA meetings), sponsors of fast track products should be strongly encouraged to meet with the FDA within 60 days of receiving designation to initiate discussion, collaboration, and definition of the pathway for successful completion of the review and approval process. Through ongoing communications between FDA and the sponsor, agreement should be reached early in the development process as to the design and conduct of a clinical study adequate to support approval for the sponsor's proposed indication.

The IND process for fast track drugs should be highly interactive and facilitate speedy development and review. Sponsors should be encouraged to define and seek agreement on the milestones in the clinical development and review process, and they should provide a general schedule to FDA. FDA should prepare to receive deliverable documents in accordance with this schedule and initiate appropriate review very quickly thereafter. FDA should perform a preliminary analysis of submitted safety and efficacy data that is sufficient to detect, and fix, problems early.

A general schedule containing major action dates should be agreed upon as early as possible. Sponsors who anticipate that they will be unable to submit documents in accordance with the schedule agreements should be required to notify FDA at least 30 days before major milestones and 14 days before minor milestones (consistent with submission deadlines for Type A, B, and C meetings established as a part of PDUFA-2 performance goals) in order to re-negotiate the schedule, as well as to ensure sufficient advance notice to FDA for staff time to be reprogrammed.

Sponsors of fast track products should be strongly encouraged to seek protocol agreements, as provided under PDUFA-2 performance goals, both for pivotal trials and Phase IV studies (as appropriate), as early in the clinical trial process as possible. FDA should exercise reasonable flexibility in its review of the adequacy of fast track product protocols and should make best efforts to reach speedy agreement with the sponsor, beating the 45-day PDUFA-2 performance goal whenever possible.

If it is necessary to change protocols or experimental procedures during the course of a study or experiment, it is expected that the sponsor will propose, and the FDA will review and respond to, such changes in a timely fashion.

NDA/BLA Submission Process

An important feature of the fast track system is to facilitate early review and decisions about a product prior to the submission of a complete application package. With this approach, final action on the application should require only a minimum amount of time and primarily involve administrative matters and final label review.

This "rolling review" mechanism is triggered upon by FDA's preliminary review of portions of an application and conclusion that the product is likely to be approvable.

The Agency should establish an information system to enable new drug sponsors to determine the status of their NDA/BLA at any time after the preliminary review and acceptance of one or more portions of their application. The reviewing division should give priority to the handling of the fast track submissions over non-fast track submissions. This means that the Primary reviewer should be required to review the sponsor's documentation either immediately upon receipt or upon completion of review of earlier-received documents for other fast track products.

Standards for Marketing Approval and Post-Approval Issues

Standards for Marketing Approval

As discussed in the earlier section on surrogate endpoints, fast track products that are approved on the basis of their effect on a clinical endpoint or validated surrogate endpoint should receive a conventional approval and not be subjected to the postapproval requirements contained in subsection (b)(2).

Subsection (b) represents an alternative basis for approval that is applicable to products approved on the basis of a "clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit." We believe that Congress intended this reference to apply to unvalidated data that is reasonably likely to predict clinical benefit, regardless of whether such data consist of a surrogate or clinical endpoint.

For example, consider a fast track product for which the pivotal trial studied a clinical endpoint and produced a confidence interval of 93%. Under current policy, such products are non-approvable because, in the absence of demonstrating a 95% probability that the clinical benefit was due to the drug and not chance, efficacy is considered unproved.

We believe that, in cases like this one, subsection (b) approval is appropriate. A study with a 93% confidence interval is "reasonably likely to predict clinical benefit," even though it does not prove such benefit in accordance with accepted scientific standards. A subsection (b) approval, combined with a postapproval study requirement to validate efficacy in a properly powered study, is appropriate in this situation.

As this example suggests, we encourage FDA to carefully consider whether, given the limitations of alternative therapies, evidence of safety and efficacy is sufficient to apply subsection (b). A similar standard, though beautifully articulated in FDA's Subpart E regulation, is more often ignored than applied. A product that has a 90% chance of being effective is always better than no product at all.

Postapproval Requirements

We urge you to note minor difference between the postapproval requirements contained in the accelerated approval regulation and those contained in subsection (b). Under subsection (b), FDA *may* --but is not mandated to--require Phase IV studies and/or preapproval of marketing literature. Furthermore, as discussed in the House Report on this legislation, Congress anticipates that FDA will preapprove marketing literature for such period of time as is necessary to establish that the sponsor understands the Agency's requirements with respect to such literature, and not until completion of any required Phase IV study (as is typically the case for accelerated approval products). We believe that, in the absence of a pattern of inappropriate promotional activities, preapproval of promotional literature should automatically terminate six months after product approval.

General Guidance

In addition to the issues discussed above, we believe that FDA's fast track guidance document should discuss the following issues with respect to surrogate endpoints:

- Guidelines for the selection of surrogate endpoints in serious diseases (comparable to the guidance document describing when a single clinical trial is adequate to support approval);
- Guidelines as to the use of professional societies, scientific advisory boards, and consultants in the development of surrogate endpoints;
- Guidelines on whether and when validated quality-of-life scales can be utilized as primary clinical endpoints; and
- Dissemination of information concerning the acceptability of specific surrogate endpoints (comparable to the recent guidance document on tumor shrinkage as a surrogate endpoint for solid tumors).

Appendix A

Definition of "Serious and Life-Threatening Condition"
Source: H.Rep. No. 105-310, at 55-56 (1997)

"The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency deficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel diseases, asthma, rheumatoid arthritis, diabetes mellitus, systematic lupus erythematosus, depression, psychoses, and many other diseases can be serious for certain populations in some or all of their phases."

POINTS TO CONSIDER

for

The development of policies, procedures and multicenter guidance documents related to off-label information under the FDA Modernization Act of 1997 (FDAMA)

June 1998

Prepared by
Massachusetts Biotechnology Council (MBC)

FDA Modernization Act (FDAMA)
§401: Off-label Information
Points to Consider

Introduction

Section 401 of the FDA Modernization Act of 1997 (FDAMA) permits the dissemination of information on unapproved uses (off-label uses) subject to a variety of limitations and requirements. The FDA issued a Proposed Rule on June 8, 1998 (*see* 63 Fed. Reg. 31143). Section 401 becomes effective on November 21, 1998, or upon the issuance of a final regulation, whichever is sooner.

The MBC has reviewed working drafts of *PhRMA's Recommended Approach to the Implementation of the Treatment Information Dissemination Provisions of the FDA Modernization Act (§ 401)*, which is being prepared by the Pharmaceutical Research and Manufacturers of America (PhRMA). The MBC generally supports the proposals it has reviewed. We anticipate reviewing the version actually submitted to FDA by PhRMA, comparing PhRMA's recommendations and the FDA's Proposed Rule, and issuing supplemental comments responsive to the specifics of both documents at that time.

Discussion Points

The MBC is in the process of reviewing the recently proposed regulations by the FDA implementing section 401 of FDAMA.

The MBC anticipates submitting its comments on said regulations under separate cover in the near future.

POINTS TO CONSIDER

for

The development of policies, procedures and multicenter guidance documents related to health care economic information under the FDA Modernization Act of 1997 (FDAMA)

June 1998

Prepared by
Massachusetts Biotechnology Council (MBC)

Concerns with Enactment of the Food and Drug Administration Modernization Act of 1997

Working Group Discussions Regarding

Section 114. Health Care Economic Information

Congress has expressly recognized that the market realities of contemporary health care make health care economic information essential for the commercialization of life science. *See* Food and Drug Administration Modernization Act (FDAMA), § 114, Pub. L. 105-115, 111 Stat. 2296 (Nov. 21, 1997). In an era of managed care, consolidation among providers that increases their negotiation power with drug manufacturers, and greater reliance upon formularies, costs do matter. Health care insurers are calling for economic data and, increasingly, the life science sector must provide this data to obtain reimbursement for its products.

The MBC has reviewed the *Guidance for Industry: Promotional Use of Health Care Economic Information Under Section 114 of the Food and Drug Modernization Act,* which was submitted by the Pharmaceutical Research and Manufacturers of America (PhRMA) to the FDA (see following document). The MBC supports PhRMA's position on § 114 of FDAMA and urges the FDA to adopt PhRMA recommendations. We anticipate reviewing the version actually submitted to you by PhRMA and issuing supplemental comments at that time.

PhRMA

June 22, 1998

Ms. Minnie Baylor-Henry
Director, Drug Marketing, Advertising
and Communications Division
Office of Drug Evaluation I, CDER
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Promotional Use of Health Care Economic Information – Recommended Approach for Implementing FDAMA §114

Dear Ms. Baylor-Henry:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry input on Section 114 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.

As you know, FDAMA §114 amends Section 502(a) of the Food, Drug, and Cosmetic Act to allow health care economic information (HCEI) that directly relates to an approved indication to be provided to formulary committees or similar entities, so long as such information is based on "competent and reliable scientific evidence." This provision, which took effect February 19 of this year, was intended by Congress to provide significant new authority for the provision of HCEI to managed care or other similar health care providers with drug selection responsibility.

PhRMA's Pharmacoeconomic Work Group, with the assistance of the PhRMA Health Outcomes Work Group (HOWG), prepared the attached recommended Guidance For Industry. Considerable professional experience in the HCEI outcomes discipline was brought together in this effort to assist FDA in implementing this important new provision, and also to assist our members in utilizing it. The Pharmacoeconomic Work Group is available at your convenience to discuss this recommended approach. We hope that you and

others at FDA, and interested members of the public, find this input useful, and that the Agency makes it widely available.

Sincerely yours,

Timothy R. Franson, M.D.
Vice President, Clinical Research and
Regulatory Affairs – U.S., Eli Lilly and Company
Chair, PhRMA Pharmacoeconomic Work Group
317/277-1324

Jean-Paul Gagnon, Ph.D
Director, Health Outcomes Research Policy
Hoechst Marion Roussel
Chair, PhRMA HOWG

Russel A. Bantham
Senior Vice President and General Counsel
PhRMA

cc: Jane Axelrad, Associate Director for Policy, CDER/FDA

GUIDANCE FOR INDUSTRY[1]

Promotional Use of Health Care Economic Information

Under Section 114 of the

Food and Drug Modernization Act

I. Introduction.

Under section 502(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), a drug is deemed to be misbranded "if its labeling is false or misleading in any particular." (21 U.S.C. § 352(a)). Section 114 of the Food and Drug Administration Modernization Act ("FDAMA") (PL 105-115) amends section 502(a) to specify "health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health

---

[1]This guidance has been prepared by FDA's Division of Drug Marketing, Advertising and Communication. This guidance represents the agency's current thinking on promotional use of health care economic information. It does not create or confer any rights for or on any person and does not operate to bind FDA or the industry. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence."

Although section 114 of the FDAMA changes significantly the standard for the Food and Drug Administration's (FDA) review of promotional materials that comprise health care economic information ("HCEI"), it does not affect other, existing regulatory standards outside that context. The new standard affects only FDA's review of promotional materials under section 502(a) of the FFDCA. It does not change established rules and FDA policies governing dissemination of information on drug prices (e.g., 21 C.F.R. § 200.200), promotional use of other information about a drug or the dissemination of information, including HCEI, in a non-promotional context, such as manufacturer responses to unsolicited requests for information about a drug or industry-supported scientific and educational activities. See "Final Guidance on Industry-Supported Scientific and Educational Activities." 62 Fed. Reg. 64074 (December 3, 1997). This also does not affect the agency's current guidances on dissemination by drug manufacturers, of certain reprints of journal articles and reference texts (medical textbooks and compendia) which contain information concerning FDA-approved products that may not be consistent with approved labeling for the products, entitled "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry Funded Dissemination of Reference Texts." 61 Fed. Reg. 52800 (October 8, 1996).

The agency is providing this guidance to describe the agency's policy for reviewing promotional materials comprising HCEI under section 114 of the FDAMA. This

guidance seeks to clarify the agency's interpretation of several terms included in section 114, to describe the process for submission and review of promotional materials comprising HCEI, and to describe the criteria FDA will use to determine whether or not promotional materials comprising HCEI meet the competent and reliable scientific evidence standard for substantiation.

II. Background.

A. History of FDA Regulation of Pharmacoeconomic Information.

Increasingly, HCEI is becoming an important part of the information used by managed care organizations, integrated delivery systems, and other organizations to make drug selection decisions. At the October 1995 FDA public hearing "Pharmaceutical Marketing and Information Exchange in Managed Care Environments," several representatives from managed care pharmacy backgrounds described the need for health care economic information and their use of those data. Richard Jay, Pharm. D., Vice President Corporate Pharmacy Services, FHP, Inc. (a mixed group-independent practice association model managed care organization with nearly 2 million members) stated:

> [A]ccess to valuable and meaningful outcomes, cost-effectiveness information spanning entire episodes of medical care could prove extremely valuable. Such information provided by a pharmaceutical company could lead to improvement in quality and reduced cost for a managed care organization, as well as the health care industry in general.
>
> ...
>
> Regardless of what is ultimately decided with respect to the way the kinds of information in question are communicated, it is incumbent upon the managed care organization itself, or other

recipient of the information to develop systems internally, structures and processes by which they can evaluate this information internally, so that they can come to their own meaningful conclusions on drug therapy decisions.

James Lang at ValueRx, a pharmacy benefit management company, summarized the problems his organization faces in making decisions about drug therapy:

> The types of information we put before the [Pharmacy and Therapeutics Committee] and evaluate internally include Phase 3 and Phase 4 and post-marketing clinical trials; manufacturer-supplied information; when available, academic clinical trials; medical texts; drug compendia; articles from peer-reviewed and scientific publications; presentations and proceedings from medical meetings; and, if available, national benchmarks and published guidelines.
>
> The problem with most of this information, from our perspective, is that the clinical trial data in particular is of an artificial environment and not a real life situation, which makes it very difficult to make decisions that impact real life utilization of the drugs; and including strict inclusion and exclusion criteria that don't really categorize or adequately describe the population that these drugs are going to be used in; and, in particular, no comprehensive pharmacoeconomic data is included.
>
> The types of pharmacoeconomic –the situation in our environment for pharmacoeconomic evaluation is really very, very limited data is available, considering the broad number of categories that need to be evaluated. The reality of the fact is that managed care makes pharmacoeconomic decisions on a daily basis, and because the data is unavailable, oftentimes treat this in a cost minimization mode where they treat most drugs as if they were equivalent, which may or may not be the case.
>
> The types of information that we really need are more realistically designed outcome studies, with economic data included and involving a broader category of costs and scope of costs, and then particularly outcome for all patients, and the cost of treatment failures and the cost of that therapy that is required because of that treatment failure.

As a consequence, pharmaceutical companies are conducting studies and analyses to provide those data. According to the Senate Report accompanying FDAMA, "Health economic information about approved 'on label' uses is needed by managed care experts and other health care providers responsible for evaluating the benefits, other consequences, and costs of competing therapies. Health care providers also rely on companies to conduct studies in the providers' own or comparable representative populations to help the providers predict the specific benefits and costs of FDA-approved products for their particular organizations." S. Rep. No. 105-43, at 42-43 (July 1, 1997). This citation accords with the House Report, which states: "The type of health care economic information that can be provided pursuant to this section is that which is directly related to an approved labeled indication." (H.R. Rep. No. (105-310, at pp. 65-66).

As pharmaceutical companies expanded their use of HCEI, by the mid-1990s FDA's role as a regulator became an important issue. The agency began considering how to apply economic information to the statutory requirement under section 502(a) that information not be false or misleading. The law clearly permitted the assignment of costs to clinical outcomes demonstrated by adequate and well controlled clinical trials. But the agency also had to assess whether the statute permitted a whole range of economic approaches to evaluating resource utilization findings shown in observational studies to flow from outcomes that are demonstrated by adequate and well controlled trials.

To address these issues, in March 1995, FDA's Division of Drug Marketing, Advertising and Communications released its Draft Principles for the Review of Pharmacoeconomics at a public workshop on comparative effectiveness, safety, and cost-effectiveness. In October 1995, FDA held the above-referenced public hearing as its "first formal step in developing policies to assure that health care decision makers have access to the information they need to make the best possible decisions and that the public health is protected at the same time by assuring that false or misleading promotional information does not become the basis for medical decision making." (Statement from Janet Woodcock, M.D., Director, Center for Drugs Evaluation and Research) In November of 1996, a Public Health Service Task Force presented its views at a workshop on Cost Effectiveness in Health and Medicine. The internal FDA discussions stimulated by these public meetings continued during 1997, but it soon became clear that Congress might address the issue in legislation.

B. Congressional Action.

Congress did address the issue in section 114 of FDAMA. In drafting that section, the Senate noted the importance of HCEI, and expressed the view that the flow of such information should increase. S. Rep. No. 105-43, at 42-43. In particular, the Senate noted that the "two clinical trial" substantiation standard inhibited the sharing of useful information. Id. The Senate Report states:

> The committee believes that the FDA should allow companies to share health economic information about approved "on label" uses for products under the same standard applied to over-the-

> counter drugs and other products. The agency currently requires these claims—which differ from efficacy claims—to be subjected to two clinical trials. The agency on several occasions conceded that this standard is inappropriate for such claims and agreed that it should be modified to a more appropriate standard.
>
> ...
>
> The FDA should not unduly impede the flow of that information to experts who need it for patient and health plan decisions. Undue restrictions on the ability of companies to make competent and reliable claims on the basis of cost, effectiveness, or safety of approved uses of products interfere with the public health by encouraging the sale and use of needlessly expensive products.

Id. Rather than simply change that standard across the board, however, Congress took a different approach.

For certain types of messages provided to certain audiences, as described more fully below, Congress sought to impose a more flexible and less restrictive substantiation standard consistent with the 'directly related to an approved labeled indication' language in the House Report. To achieve the greater flow of information that Congress desired, Congress adopted by reference the standard of substantiation employed by the Federal Trade Commission ("FTC") for over-the-counter pharmaceutical marketing. See S. Rep. No. 105-43, at 3-4 and H.R. Rep. No. 105-310, at 65-67. To define the types of information and permitted audience, Congress: (1) limited the type of information that could be disseminated under the competent and reliable scientific evidence standard to HCEI directly related to an approved labeled indication, and (2) limited the audience to whom information could be disseminated under that standard to formulary committees or similar entities responsible for selecting drugs for managed care or other similar organizations. 21 U.S.C. 352(a). That audience comprises those who have

more expertise in evaluating drug therapies than patients or health care providers not involved with those activities. See, S. Rep. No. 105-43, at 3-4 ; H.R. Rep. No. 105-310, at 65-67. These limitations on the dissemination of information under section 114 provide safeguards for the more flexible and less restrictive evidence standard imposed by that section.

The analysis of the impact of section 114 starts with the premise that Congress intended to increase the flow of information between manufacturers and managed care decision-makers with respect to health care economic analyses. See, S. Rep. No. 105-43, at 42-43; H.R. Rep. No. 105-310, at 65-67. As a consequence, the promotional activity now permitted under Section 114 must go beyond previous FDA policy that permitted promotional dissemination of HCEI which simply assigns dollar values (or other cost measures) to outcomes proved by adequate and well controlled trials, to encompass outcomes and costs collected outside of adequate and well controlled trials, but still directly related to the labeled indication.

We also start with the rule of statutory construction that the Act must be read to give meaning to all parts of the statute including the restrictions imposed on the use of HCEI (i.e., the scope of that term, the limits on the permitted audience, and the requirement in the House Report that the information be directly related to an approved labeled indication). Reading those restrictions in tandem with the goal of increasing the flow of information leads to the inference that the substantiation standard Congress borrowed from FTC was intended to be less restrictive than the prior standard that applied to all information conveyed in promotional labeling and advertising for prescription drugs, including HCEI. Such a reading gives meaning

to the statutory restrictions because it means that Congress placed parameters around the information that would be subject to this new, less restrictive standard.

Congress recognized that HCEI inherently includes comparative clinical information and other extensions from data based on adequate and well controlled clinical trials using reasonable assumptions about health care economic consequences. In the House Report, five examples are provided: rheumatoid arthritis; heart failure, Type I diabetes; osteoporosis; and meningitis associated with haemophilus b influenza vaccination. See, H.R. Rep. No. 105-310, at 65-67. Given (1) the goal of Congress to increase the flow of information from pharmaceutical companies to managed care entities, (2) the restrictions that Congress placed on the process for providing that information and (3) the fact that prior law already permitted the mere assignment of costs to clinical outcomes proven through substantial evidence, Congress apparently intended to apply the less restrictive substantiation standard to the various elements of HCEI directly related to an approved labeled indication, including the comparative clinical information and other extensions beyond data based on adequate and well controlled clinical trials. To clarify that, the House Report explains that "Incorporated into economic consequences are the costs of health outcomes. Data about health outcomes associated with the use of a drug, other treatments, or no treatment are therefore incorporated into the economic analysis." H.R. Rep. No. 105-310, at 65-67. Thus, Section 114 allows dissemination of those data—even where the substantiation for the clinical data underlying the HCEI may involve methods other than adequate and well-controlled trials—as long as the data are (1) part of an economic analysis supported by competent and reliable scientific evidence, (2) directly related to an approved indication and (3) disseminated under the other limitations noted above.

C. FDA Reviews of Promotional Materials.

Since Congress only sought to address the use of HCEI in the promotional context, in section 114 Congress left undisturbed other rules and regulatory policies that FDA has developed for such information issues as industry support of scientific and educational symposia and unsolicited requests for product information. Because section 114 was effective on February 19, 1998, without the need for implementing regulations, since that time FDA administered the new provision through its process for collecting promotional labeling and advertising at the time of first use for drug products subject to a new drug application. When FDA examines promotional materials it receives, the agency must distinguish between HCEI and all other types of promotional materials. The agency thus applies the competent and reliable scientific evidence to HCEI under Section 114, and the substantial evidence test to most other types of information.

D. FDA's New Standard for Substantiating HCEI.

1. FTC Origins of the Standard.

For information that meets the definition of HCEI and satisfies the other limitations specified in the statute, to encourage pharmaceutical companies to share more information than they have been able to in the past, section 114 requires that the information be

substantiated by competent and reliable scientific evidence as that term is used by the FTC. According to the Senate Report:

> This provision differentiates between clinical claims and economic claims. Clinical claims would continue to be governed by the evidence standard in the Act. Economic claims would be governed by the "competent and reliable scientific evidence standard used by the Federal Trade Commission, drawing from available evidence in the relevant economic fields of science."

S. Rep. No. 105-43, at 42-43. Thus, Congress explicitly borrowed the FTC standard of substantiation, and applied it to HCEI regulated by FDA. The House Report more specifically explains:

> The standard of competent and reliable scientific evidence (49 Fed. Reg. 3099) (August 2, 1984)) supporting health care economic information provided under this subsection takes into account the current scientific standards for assessing the various types of data and analyses that underlie such information. Thus, the nature of the evidence required to support various components of health care economic analyses depends on which component of the analysis is involved. For example, the methods for establishing the economic costs and consequences used to construct the health care economic information would be assessed using standards widely accepted by economic experts. The methods used in establishing the clinical outcome assumptions used to construct the health care economic analysis would be evaluated using standards widely accepted by experts familiar with evaluating the merits of clinical assessments. In addition, the evidence needed could be affected by other pertinent factors.

H.R. Rep. No. 105-310, at 65-67.

As already noted, Section 114 incorporates the FTC standard using the phrase "competent and reliable scientific evidence." When enacting the new FDA standard, Congress borrowed that FTC phrase, including the word "scientific," defining that agency's standard for

substantiation of claims involving scientific data. For example, FTC used this exact standard in its regulation covering environmental claims in 16 C.F.R § 260.5. In describing its evidential standard for advertising general goods and services such as clothing and toys, FTC officials typically use the phrase "competent and reliable evidence". When talking about goods such as pharmaceuticals that implicate science, FTC officials typically use the more specific phrase of "competent and reliable scientific evidence."[2]

2. Meaning of the Standard in FTC Orders.

In recent years, the FTC's Orders in most drug cases define the phrase "competent and reliable scientific evidence" as "tests, analysis, research, studies or other

---

[2]While the following methodology has its limitations, to determine what phrase FTC uses in its orders to reference its substantiation standard for drugs, one could search in the LEXIS - Trade - FTC computer database. This database contains all FTC orders since 1950. Court decisions are not included. We tested to find out which of the following phrases-- "competent and reliable scientific evidence" and "competent and reliable evidence"—FTC uses more often in the drug context. The following are the search results as of 2/10/98.

Search 1:	("competent" within one word of "reliable" within one word of "scientific") and (drug or pharmaceutical)
Results:	**297** FTC orders were responsive.
Notes:	We have checked a good sample of the responsive cases, and this search definitely picks up the phrase "competent and reliable scientific evidence." It also picks up any mention of the "Food and Drug Administration", so it is possible that not all of the responsive cases concern drugs.
Search 2	("competent" within one word of "reliable" within one word of "evidence") and (drug or pharmaceutical)
Results:	**110** FTC orders were responsive
Notes:	This search does pick up the phrase "competent and reliable evidence." It also picks up cases in which both phrases appear.

evidence based on the expertise of professionals in the relevant area that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted by others in the profession to yield accurate and reliable results." *E.g. Herbal Ecstasy* (OTC psychotropic drug) - In re Global World Media Corporation, 1997 FTC *Lexis* 314 (Oct. 17, 1997); *Bonebuilder* (OTC calcium supplement) - In re Metagenics, Inc., 1997 FTC *Lexis* 313 (Oct. 31, 1997); *Venoflash* (treatment for circulatory system blockage, varicose veins and hemorrhoids) - In re Efficient Labs, Inc., 1997 FTC *Lexis* 303 (Sept. 12, 1997); *Nutriol* (OTC topical hair treatment) - In re Nuskin International, Inc., 1994 FTC *Lexis* 322 (April 1, 1994); *Y-Bron* (anti-impotency drug) - In re Michael S. Levey, 1993 FTC *Lexis* 240 (Sept. 23, 1993); FTC also has applied the same definition in a fairly large number of cases involving weight loss products. *NutraTrim* - In re Kave Elahie d/b/a M.E.K. International, 1997 FTC *Lexis* 308 (Sept. 19, 1997); *Superformula Reductora* - In re Rogerio Monteiro, 1997 FTC *Lexis* 307 (Sept. 12, 1997); *Svelt-patch* - In re 2943174 Canada, Inc., d/b/a United Research Center, Inc., 1997 FTC *Lexis* 163 (June 16, 1997); *Fat Burners* - In re Amerifit, Inc., 1997 FTC *Lexis* 128 (June 16, 1997); *SeQuester* - In re KCD Holdings, Inc., 1996 FTC *Lexis* 737 (Dec. 18, 1996); *Ensure* products - In re Abbott Laboratories, 1996 FTC *Lexis* 707 (Dec. 23, 1996); *Nu-Day Diet Program* - In re Nu-Day Enterprises, Inc., 1992 FTC *Lexis* 105 (Apr. 22, 1992).

3. Meaning of the Standard in FTC Statements.

According to the FTC's policy statement on advertising substantiation (49 Fed. Reg. 30999 (August 2, 1984)) expressly referenced in the House Report on FDAMA (H. R. Rep. No. 105-310, at 65-67), FTC's standard for prior substantiation can be summarized as follows:

> Many ads contain express or implied statements regarding the amount of support the advertiser has for the product claim. When the substantiation claimed is express (e.g., "tests prove", "doctors recommend", and "studies show"), the Commission expects the firm to have at least the advertised level of substantiation. Of course, an ad may imply more substantiation than it expressly claims or may imply to consumers that the firm has a certain type of support; in such cases, the advertiser must possess the amount and type of substantiation the ad actually communicates to consumers.
>
> Absent an express or implied reference to a certain level of support, and absent other evidence indicating what consumer expectations would be, the Commission assumes that consumers expect a "reasonable basis" for claims. The Commission's determination of what constitutes a reasonable basis depends, as it does in an unfairness analysis, on a number of factors relevant to the benefits and costs of substantiating a particular claim. These factors include: the type of claim, the product, the consequences of a false claim, the benefits of a truthful claim, the cost of developing substantiation for the claim, and the amount of substantiation experts in the field believe is reasonable. Extrinsic evidence, such as expert testimony or consumer surveys, is useful to determine what level of substantiation consumers expect to support a particular product claim and the adequacy of evidence an advertiser possesses.

This approach to deciding the level of substantiation required necessitates a new approach by FDA for review of promotional materials involving HCEI. Rather than prescribing the specific methods by which HCEI must be obtained, the FTC standard incorporated into

section 114 is a flexible one that allows for variation in the types of evidence that are adequate to meet the statutory burden depending upon the facts and circumstances of each case. The factors FTC lists in its notice are important to the FTC standard, and involve areas that FDA has not previously considered when determining whether or not there is substantial evidence to support promotional claims. For example, the FTC's explanation of its standard expressly identifies the cost of substantiating a claim as a factor to be weighed against the benefit of the information to the audience.

In the context of HCEI, the burden to conduct additional controlled clinical trials—beyond those adequate and well-controlled trials already conducted to support the labeled indication—to demonstrate economic endpoints may be substantial. Economic endpoints generally show greater variability than efficacy endpoints; therefore studies to obtain HCEI often need to enroll larger numbers of patients to obtain significant findings. Important economic endpoints often require substantial time periods for follow up; therefore, studies to obtain HCEI may continue for long periods of time before results can be obtained. In addition, once controlled trials are completed showing the efficacy of a therapy, it may be more difficult to obtain provider or patient consent to participate in randomized controlled trials.

Other factors included in the competent and reliable scientific evidence standard as described in the FTC notice involve the nature of the claim and how the information is to be used. To an extent, Congress already dealt with these issues in defining the scope of section 114. By limiting the information to HCEI that reflects an approved labeled indication and by limiting the audience to those selecting drugs for groups, Congress limited the risk that insufficient

clinical information would be used as a basis for specific treatment decisions. In addition to those statutory parameters, the competent and reliable scientific evidence standard specifically requires balancing the benefits of a truthful claim with the consequences of a false claim under the facts of each case. Thus, in the context of HCEI, a person weighing those factors must consider that (1) HCEI is limited to approved labeled indications (i.e. those for which safety and effectiveness have been proven by substantial evidence), and (2) in order for an economic claim to drive a health care decision, the clinical factors generally need to be acceptable on their own merits.

In the FTC's Federal Register notice, the FTC also explains how it determines which claims the promotional material makes. Promotional materials make express claims that the materials spell out, but they also might imply claims without stating them expressly. According to the FTC: "One issue the Commission examined was substantiation for implied claims. Although firms are unlikely to possess substantiation for implied claims they do not believe the ad makes, they should generally be aware of reasonable interpretations and will be expected to have prior substantiation for such claims. The Commission will take care to assure that it only challenges reasonable interpretations of advertising claims." 42 Fed. Reg. at 30,999. This is an important element of FTC's standard.

Significantly, FTC encourages comparisons in advertising to facilitate competition and ensure that the market place receives the information that it needs to make choices. Indeed, the FTC prohibits standards of substantiation adopted by industry associations that require higher substantiation for comparative claims than for unilateral claims. 16 C.F.R §

14.15. Thus, in transferring the FTC standard to FDA, FDA will be careful to ensure that the application of the competent and reliable standard facilitates —rather than discourages — comparative claims .

4. Meaning of the Standard in FTC's Comments on Managed Care Promotion.

The FTC has interpreted the competent and reliable scientific evidence standard in the context of promotion of prescription drugs to managed care customers on the basis of "economic claims." In a comment letter dated January 16, 1996 to FDA, FTC explained how it regulates economic claims relating to pharmaceuticals. According to the comment letter, "[A] number of factors influence the type of evidence required for substantiation of advertising claims under the FTC's substantiation policy. One important factor is the relevant professional standards appropriate to judge the evidentiary support for the type of claim at issue. Under this approach, the required level of substantiation for economic claims for pharmaceutical products, such as cost-benefit or cost-effectiveness claims, would depend on the content of the claim made."

In its comment, FTC offered specific advice on the types of data required to substantiate these economic drug claims:

> A variety of field and other types of data are used in assessing economic questions, including cost-benefit and cost-effectiveness questions. While controlled trial data are often

> desirable for assessing certain types of questions, economic practice would not necessarily require such data for assessments of cost-benefit issues in general or of health issues in particular. In part, this reflects the high cost and long time lag necessary for collecting this type of data in many circumstances. It also reflects the fact that actual use experience can deviate from the experience observed in controlled trials due to potential biases in controlled trial data and to the different conditions in actual doctor-patient interactions, as described below.
>
> For economic questions, the literature suggests that differences in the outcomes from controlled trials and actual experience can be important in predicting behavior and in estimating the costs and benefits of various health care options. For instance, in the pharmaceutical context, side effect or convenience differences between drugs can significantly affect the likelihood that physicians and consumers will stay with a particular drug treatment. Controlled trials, in which compliance is tightly restricted for the duration of the trial in order to get a better measure of efficacy, can give substantially different results than would be found in a clinical setting, where continuation of treatment is more likely to vary with characteristics of the drug. Similarly, the literature suggests that behavioral results can be substantially affected by randomization bias, a type of selection bias that occurs when random assignment causes the type of person participating in the trial to differ from the type of person who would receive the drug in the normal clinical setting. As a result, controlled trial data can sometimes predict actual clinical implementation poorly. In this type of situation, experience with the drug in a field setting may substantially add to the available knowledge based on trial data, or may actually give superior information about economic and effectiveness issues in actual practice to that provided by a controlled trial. Such data may also raise questions about the results from controlled trials.

At the end of its comment, FTC offered as its advice to FDA the notion that insistence on substantial evidence would preclude the use of important, truthful data. In particular, FTC urged:

Depending on how it is interpreted and applied, the FDA statement in the Federal Register notice that all 'effectiveness' elements of cost-effectiveness claims must be based on adequate and well-controlled studies" could result in the prohibition of many truthful, non-deceptive claims describing the cost-effectiveness or cost-benefit characteristics of pharmaceutical products in actual treatment settings. Claims substantiated by competent and reliable epidemiologic, administrative, or other clinical data would appear to be prohibited under this standard. Claims based on shined data from HMOs or other insurers nationwide would also appear to be excluded.

If an economic claim clearly discloses the nature of the result and the data on which it is based, and the data are competent and reliable, it could provide truthful, non-misleading information to professional and insurance customers. Accurate economic claims based on actual experiences in the field, particularly when directed to these types of audiences, do not appear to us to be inherently deceptive or otherwise misleading.

Thus, FDA may wish to consider a more flexible substantiation standard for economic claims for pharmaceutical products, for instance, one requiring "competent and reliable evidence" to support the claim that is made, without an *a priori* specification as to the type of evidence required. Such a reasonable basis standard could be effective in limiting deceptive claims without having the undesirable effect of preventing truthful economic claims. In some instances, controlled trial testing may be the appropriate type of substantiation for a particular type of economic claim, as when an efficacy claim is included, but in other circumstances other types of evidence might constitute appropriate substantiation.

E. Limitations on the Scope of Section 114.

1. Directly Related to an Approved Indication,

In addition to fitting within the parameters of the term HCEI, section 114 further limits the types of messages that would qualify for this special treatment to include only

information that is directly related to an indication approved by FDA. for inclusion in the drug's labeling. In particular, amended section 502(a) states that HCEI "shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug...." It is instructive that Congress chose to emphasize the concept of labeled indication rather than the broader term "use." Although managed care decision-makers may commonly consider the inclusion on formulary of off-label uses of approved drugs, section 114 does not authorize dissemination by manufacturers of promotional information related to those uses even under the more liberal evidence burden of that section. Section 114 is limited to approved indications--i.e. those uses of an approved drug directly related to an indication approved under section 505, or section 351(a) of the Public Health Service Act.

2. The Permitted Audience.

The second limitation to the reach of section 114 involves the audience to whom manufacturers are permitted to disseminate the information. Congress made the legislative finding of fact that the professionals falling within the categories outlined in the statute have adequate expertise and experience to understand and make appropriate use of information that satisfies the competent and reliable scientific evidence test. H.R. Rep. No. 105-310, at 65-67. Although specific procedures may vary from one organization to another, those entities generally have established policies and procedures for evaluating information on drug therapies including HCEI.

Section 502(a) provides, in part, that "health care economic information [may be] provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of dregs for managed care or other similar organizations," Explaining Congressional intent with regard to that Imitation, the House Report notes that:

> The purpose of section 10 is to make it possible for drug companies to provide information about the economic consequences of the use of their products to parties that are charged with making medical product selection decisions for managed care or similar organizations. Such parties include formulary committees, drug information centers, and other multidisciplinary committees within health care organization that review scientific studies and technology assessments and recommend drug acquisition and treatment guidelines. The provision is limited to analyses provided to such entities because such entities are constituted to consider this type of information through a deliberative process and are expected to have the appropriate range of expertise to interpret health care economic information presented to them to inform their decision-making process, and to distinguish facts from assumptions, This limitation is important because it will ensure that the information is presented only to parties who have established proceduresand skills to interpret the methods and limitations of economic studies, The provision is not intended to permit manufacturers to provide such health care economic information to medical practitioners who are making individual patient prescribing decisions nor is it intended to permit the provision of such information in the context of medical education,

H.R. Rep. No 105-310, at 65-67,

In limiting the audiences that could qualify for this special treatment, section 114 adopts the FTC approach to determining required levels of substantiation based upon the target audience. Audience plays an important role in the substantiation required under the FTC's competent and reliable scientific evidence standard. The FTC commented on the importance of the audience considerations in its letter to FDA on promotion to managed care. According to FTC, "As noted in the FDA's *Federal Register* notice, many economic claims are likely to be directed to HMOs, physicians, insurers, and employer-insurers. . . . We would encourage consideration of the view that the relevant audience for any claim should play a central role in identifying the claims made and assessing whether those claims are likely to be deceptive to that audience."

This is not new to FDA, of course. Courts have repeatedly held that compliance with section 502(a) should be judged by the meaning of the words to the audience to which the labeling is directed. United States v.23. More or Less. Articles, 192 F.2d 308, (2d. Cir. 1951); V. E. Irons v. U.S., 244 F.2d 34 (1st. Cir. 1957), cert. denied 354 U.S. 923 (1957); U.S v. Vrilium Products Co., 1938-1964 F.D.L.I. Jud. Rec. 944 (N.D. Ill. 1950), affirmed 185 F.2d. 3 (7th Cir. 1950). In line with that test, courts have interpreted section 502(a) as imposing a higher burden for substantiation when the audience is unsophisticated. E.g., United States v. Ten Cartons, More or Less, 1938-64 F.D.L.I. Jud. Rec. 1519 (1957); United States v. Hoxsey Cancer Clinic, 198 F.2d 273 (5th Cir. 1952); United States v. Vitamin Industries, Inc., 130 F. Supp. 755 (D. Neb. 1955); United States v. Articles of Drug . . . "Vit-RA-Tox", 263 F. Supp. 212, (D. Neb. 1967). The converse is also true--the more expert the audience, the lower the burden.

III. Guidance.

Under section 114 of the FDAMA, FDA will review promotional materials comprising HCEI that are disseminated or otherwise presented to decision-makers who select drugs for managed care and similar health benefits organizations to determine whether those materials are false or misleading under a competent and reliable scientific evidence standard. Promotional materials comprising other clinical information will be reviewed under the traditional standard for substantiation of promotional claims—i.e., the substantial evidence standard.

A. Competent And Reliable Scientific Evidence.

This is a flexible standard for assessing the adequacy of substantiation of HCEI considering: (1) what claims are made by the HCEI and in what form the information is disseminated, (2) who is the audience, and (3) whether there is a reasonable basis to substantiate the HCEI associated with a labeled indication as determined by the availability of competent and reliable scientific evidence.

If the substantiation for HCEI is stated expressly as part of the information, the firm must have at least the stated level of substantiation. If the HCEI is inconsistent with the substantial body of competent and reliable evidence in the area, the firm must have an adequate

explanation as to why the HCEI is considered to be competent and reliable. For example, without an adequate explanation, HCEI relying solely on the results of one small study would not be substantiated by competent and reliable scientific evidence if those findings are contradictory to results found in a large number of large well-designed studies. On the other hand, a single well-designed and conducted study that is directly related to an approved indication could provide competent and reliable substantiation for HCEI in the face of contrary evidence from poorly designed studies.

Where the substantiation for the HCEI is not stated expressly as part of the information, the following factors would be considered to determine whether there was competent and reliable scientific evidence to support the HCEI:

- Type of claim:—e.g., cost savings, cost-effectiveness, other forms of economic measure
- Nature of the product: —i.e., the condition for which a drug is used or the setting in which it is provided or used.
- Consequences of a false claim: —e.g., the degree of economic harm.
- Benefits of a truthful claim. —e.g., more informed decision making by those who must make decisions in real time in an uncontrolled world.
- Cost to develop different levels of substantiation for the claim:--consideration of technical and economic feasibility of conducting additional studies to substantiate the HCEI (cost, length of study, burden on patients, difficulty

As HCEI is generated using methods from a relatively young and dynamic discipline, it would not be appropriate to prescribe which methods for obtaining HCEI would be acceptable under a competent and reliable scientific evidence standard. Taking such a prescriptive approach in this guidance at this time could stifle methodologic advances in health care economics and ultimately could limit the flow of HCEI contrary to Congress's intent. Therefore, this guidance focuses on compliance with accepted guidelines for designing, conducting, and reporting findings from health care economic studies, such as those cited above.

B. Disclosure

Under section 114, FDA will focus on disclosure of material inputs and methods—an important feature of essentially all accepted guidelines in this discipline—to determine whether HCEI associated with an indication is substantiated by competent and reliable scientific evidence. While many forms of disclosure are appropriate, there are consensus approaches such as the one recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) that include useful disclosures and/or disclaimers. See "Pharmacoeconomic Modeling Disclaimer Proposed by ISPOR Panel", The "Pink Sheet", p. 8 (March 3, 1998). While health care economic information under section 114 is for promotional presentation, the ISPOR approach recommends the use of a standard disclaimer of limitations in any presentation of HCEI including journal articles and other scientific and commercial presentations based on models which rely on assumptions about a drug's efficacy.

The ISPOR approach is in harmony with the approach the agency has used in similar situations such as its "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry Funded Dissemination of Reference Texts." 61 Fed. Reg. 52800 (October 8, 1996). In its reprint guidance, FDA suggests that if a reprint contains effectiveness rates, data, analyses, uses, regimens or other information that is different from the approved labeling, the reprint should prominently state the difference(s), with specificity, on the face of the article. In addition, the guidance observes that the reprint should disclose all material facts.

The disclosure should provide information to explain the inputs, assumptions and methods made in the HCEI. Such disclosure should follow a standardized format and allow one reviewing the HCEI to determine the reliability and validity of the information and its relevance to decision making about allocation of resources. Standard formats for evaluating HCEI and underlying clinical information include those described by Stoddart and Drummond (Stoddart GL, Drummond MF. How to read clinical journals: VII. To understand an economic evaluation [parts A and B]. Can Med Assoc J. 1984;130:1428-1434;1542-1549.), Naylor and Guyatt (Naylor CD, Guyatt GH. Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. JAMA. 1996;275:554-558.), and others.

Based upon those guidelines, one should consider disclosure of the following:

1. Identification of the research question which the HCEI is addressing.

C. Directly Related To An Approved Indication.

In addition to fitting within the parameters of the term HCEI, section 114 further limits the types of messages that would qualify for this special treatment to include only information that is directly related to an indication approved by FDA for inclusion in the drug's labeling. In particular, amended section 502(a) states that HCEI "shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug...." Five examples are provided by the House Report (H.R. Rep. No. 105-310, pp. 65-66). These examples are meant to be illustrative, but not comprehensive nor restrictive.

Although managed care decision-makers may commonly consider the inclusion on formulary of off-label uses of approved drugs, section 114 does not authorize dissemination by manufacturers of promotional information related to those uses even under the less restrictive evidentiary standard of that section. Section 114 is limited to approved indications--i.e. those uses of an approved drug that involve conditions included in the approved labeling.

Examples of statements that are directly related to the approved labeled indication include, in certain cases, statements based on data involving practice settings, dosage levels actually used or prescribed, and durations of use that go beyond specific statements about those settings, dosages or durations of treatment included in the approved labeling. For example, if the labeling summarizes the results of a clinical trial conducted in a fee-for-service setting, HCEI extrapolating those findings to a managed care organization or other similar provider setting

could be directly related to the approved indication. If the approved labeling indicates a particular dosage for a drug and HCEI based upon drug utilization from a managed care organization database or a database from another provider setting includes actual patient use of the drug that may fall outside the approved dosage level, the HCEI could be directly related to the approved indication. (Drug utilization data provides the actual use of the drug, therefore, patients prescribed 25 mg of a drug bid which is labelled to be taken as 50 mg qd, may actually take 50 mg qd, 25 mg bid, 25 mg qd or 0 mg qd, and therefore, over the period covered by the DUR the daily dosage may be something other than 50 mg qd as labelled.) In this case, it may be acceptable to use drug utilization databases for HCEI. If the approved labeling summarizes the results of a clinical trial in which the clinical endpoints were assessed following 6 months of treatment, HCEI based upon competent and reliable scientific evidence covering a duration of use beyond 6 months consistent with the labeled indication could be directly related to the approved indication.

D. Health Care Economic Information.

Under section 114, HCEI "means any analysis that identifies, measures or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention or to no intervention." This definition includes all forms of economic analysis intended to facilitate decision making about the allocation of resources. Commonly used methods include, but are not limited to, cost analyses (also termed cost-consequence analyses, cost-identification analyses, or

cost-minimization analyses), cost-effectiveness analyses(including cost-utility analyses) and cost-benefit analyses.

HCEI comprises the report of an economic analysis including, as may be appropriate for a given analysis, a description of clinical and economic inputs, analysis methods, and findings. Clinical outcomes for which economic consequences may be presented in the HCEI associated with an approved indication may include physiologic, anatomic and biologic endpoints (e.g., blood pressure levels, survival rates, survival times, life expectancy, rates of myocardial infarction or stroke), health status and quality of life measures, quality adjusted life expectancy, measures of patient preference or satisfaction, or other measures relevant to decision makers.

Information on the burden of a disease (also called a burden of illness study ordinarily does not fall under the scope of the Act because ordinarily it is not labeling or advertising. Nevertheless, when burden-of-illness data does comprise advertising or labeling, FDA reviews the data to determine whether or not the data are truthful and not misleading using the competent and reliable scientific evidence standard.

Although HCEI is generally comparative in nature, information on the economic consequences of the use of a drug that is presented without comparison to another drug, another health care intervention or to no intervention would also be reviewed under the competent and reliable scientific evidence standard.

HCEI, which is disseminated to formulary or similar committees under section 114, may be disseminated in any of many forms. These include, but are not limited to, reprints of publications from peer reviewed journals, *reports* of proceedings from symposia, monographs, white papers, sections from textbooks, print or broadcast advertisements, electronic media (software and interactive media), formulary kits, and presentation materials submitted to technology assessment panels, medical advisory boards, and formulary or pharmacy and therapeutics committees.

E. Formulary Committee or Similar Entity.

This clause should be read together with the next clause: "in the course of the committee or the entity carrying out its responsibilities for the selection of drugs" to refer to any entity that has a decision making role for selection of drugs or that advises those decision-makers. This may inch-de a formulary committee, a pharmacy and therapeutics committee, a medical advisory board, technology assessment panel, or an individual, such as a medical director, provided that person or entity is responsible for the selection of drugs that may be used in a group of patients (i.e., a decision-maker selecting drugs outside a one-on-one prescribing decision by an individual physician for an individual patient) or advises decision-makers who have such responsibility.

Section 114 reflects Congress's assessment that these entities have sufficient expertise to evaluate HCEI. Sponsors disseminating HCEI are not required to assess the expertise of their target audiences in understanding HCEI.

F. Managed Care or Other Similar Organization.

This would include health maintenance organizations, preferred provider organizations, point of service plans, managed indemnity plans, independent practice associations, integrated delivery systems (including hospitals), provider sponsored organizations, pharmacy benefit management organizations and other organizations that are involved with decision making about the coverage or payment for items or services provided to patients or that are at financial risk for care provided to patients or that are responsible for the allocation of health care resources including the selection of drugs and other treatments patients may be offered.

G. Submission Process for Health Care Economic Information.

As section 114 of the FDAMA only covers promotional use of HCEI, the process for submission of HCEI is no different from that for submission of other promotional materials (i.e., as required under 21 C.F.R. § 314.81(b)(3)(i)). Prior approval is not required under Sec. 114 of FDAMA or FFDCA Sec. 502.

The submission should include the presentation of the HCEI in the form in which the information is to be disseminated (e.g., reprint of a publication from a peer-reviewed journal,

software package comprising an economic model with user manual) including package insert information, if required.

H. FDA Assessment

FDA will review the HCEI under the competent and reliable scientific evidence standard as described above. In general, where FDA finds that HCEI may not meet the competent and reliable scientific evidence standard, before issuing a violation, the agency will contact the sponsor to obtain additional information about the evidence substantiating the HCEI and the audience to which it was disseminated. If after review of the substantiating information available, FDA still concludes that the HCEI is not supported by competent and reliable scientific evidence, the agency will work with the sponsor to determine whether the information can meet the competent and reliable scientific evidence standard if the information were amended or modified in some respect, including where appropriate, through the addition of a statement of limitations or qualifications to the information.

If after review, FDA finds that HCEI may not meet the competent and reliable scientific evidence standard, it may consider appropriate consultation with experts in the disciplines comprising health economics to assess whether the HCEI has that level of substantiation which experts in the field believe is reasonable. Such consultation would be made consistent with established rules limiting disclosure of proprietary information and in compliance with relevant administrative laws and procedures.

A

General Concerns Regarding Enactment of the Food and Drug Administration Modernization Act of 1997

Harmonization and Consistency in the Handling of Drugs and Biologics

I. Background Information

It is essential that the FDA further pursue harmonization of the requirements for drugs and biologics where doing so will accelerate the approval of safe and effective new drugs and other therapies. The FDA already has recognized the need to harmonize certain of its requirements and taken action to this effect. The Agency has published a number of regulations and guidance documents aimed at minimizing the differences in the way like products and technologies are handled. *See, e.g.,* Changes to an Approved Application, 62 Fed. Reg. 39890, July 24, 1997; Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products, 61 Fed. Reg. 24227, May 14, 1996.

Nonetheless, there is a fundamental difference in the legal framework under which drugs are regulated (the Food, Drug and Cosmetic Act), as compared to biologics (the Public Health Services Act). This has created obvious differences in the requirements imposed by the FDA--notably that drugs are subject to NDA requirements and biologics to ELA and PLA requirements. Some of these regulatory inconsistencies (including those identified below under Tab B, "Increased Transparency and Accountability") impede the safe and responsible commercialization of innovative drugs and biologics.

Well over a decade ago, the FDA made a conscious decision to regulate biotechnology products without regard to their method of production. *See* Coordinated Framework for the Regulation of Biotechnology, Office of Science and Technology Policy, 49 Fed. Reg. 50856, Dec. 31, 1984. Ultimately, the requirements for drugs and biologics must be dictated be a rational approach *based upon good science* and the objective of making the most safe and effective products available to patients as quickly as possible, not by where in the Agency the product happens to be regulated.

II. Discussion Points

A. Promotion of Science

The biotech industry recognizes that CBER has employed a staff knowledgeable in life science, receptive to the promotion of life science, and capable of analyzing scientific data. To realize FDAMA's mission, namely the safe and expeditious commercialization of innovative health care products, competency at the forefront of life science is essential. Harmonization should be carried out to realize a consistent and uniform level of CBER's life science expertise throughout the Agency.

B. Personnel "Training"

As changes associated with FDAMA are introduced, they should be implemented uniformly and consistently. To accomplish this objective, FDA should train all of its personnel to respond to FDAMA-related changes in a consistent manner.

C. Subset Analysis

In February 1998, the FDA issued a Final Rule that requires subset analysis for all new drug application (NDAs). *See* Final Rule, Investigational New Drug Applications and New Drug Applications, 63 Fed. Reg. 6854-6862 (Feb. 11, 1998) (to be codified at 21 C.F.R. pts. 312 & 314). "This final rule reflects the growing recognition within the agency and the health community that: (1) Different subgroups of the population may respond differently to a specific drug product and (2) although the effort should be made to look for differences in effectiveness and adverse reactions among such subgroups that effort is not being made consistently." 63 Fed. Reg. at 6855. Pursuant to this Final Rule, subjects entered into clinical studies for drug or biological products must be tabulated by age group, gender and race. "This action is intended to alert sponsors and the FDA as early as possible to potential demographic deficiencies in enrollment that could lead to avoidable deficiencies in the NDA submission." 63 Fed. Reg. at 6856. The Final Rule also revises NDA content and format regulations. Under the Rule, NDAs must include effectiveness and safety data for demographic subgroups based upon age, gender, and race and, "when appropriate, other subgroups of the population of patients treated, such as patients with renal failure, or patients with different severity levels of the disease." *Id.*

Harmonization should be carried out to realize a consistent and uniform level of acceptance of subgroup analysis throughout the Agency. CBER should adopt this Final Rule as part of its review process.

D. Transparency

Due to differences between CBER and CDER draft document disclosure policies, the review of biologics is more transparent than the review of drugs. This inconsistency is addressed in Tab B ("Increased Transparency and Accountability").

B

Massachusetts Biotechnology Council, Inc. June 1998

General Concerns Regarding Enactment of the Food and Drug Administration Modernization Act of 1997

Increased Transparency and Accountability

I. Background Information

Operating in a more transparent and accountable manner would increase: (1) the FDA's predictability and accountability as an Agency, (2) uniformity among FDA reviewers, and (3) consistency in the treatment of applications. All of these objectives are encompassed by the scope of FDAMA; they would significantly advance FDA's new mission of cooperation. *See* FDAMA, § 406(b)(4).

II. Discussion Points

A. Draft Documents

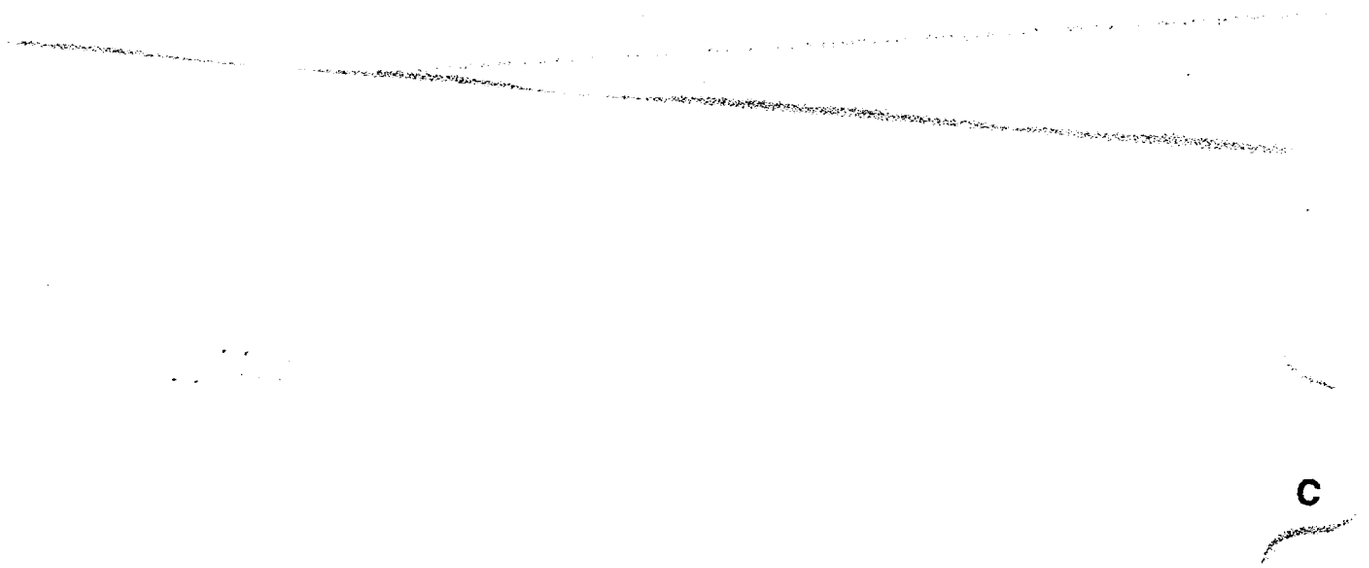
The MBC strongly supports CBER's policy of providing draft submission documents to companies before they are sent to Advisory Panels. Through this practice, CBER often offers sponsors an opportunity to prepare responsive documents and to clarify and at times improve the accuracy of the content of these submissions.

In contrast, CDER forwards submissions to Advisory Panels and the sponsoring companies at the same time. As a result, companies dealing with CDER are more likely to be taken by surprise. Moreover, the sponsor accuracy check on the information provided to Advisory Panels under CBER's policy is removed.

The MBC supports making the review process for biologics consistently transparent within CBER, and making the process for drugs (CDER) as transparent as it is for biologics. We believe that this reform would improve the quality of the information provided to Advisory Panels and enable sponsors to remain responsive, thereby enabling FDA to reach safety and efficacy determinations that are as scientifically and factually sound as possible. Therefore, the MBC proposes that FDA make CBER's policy of disclosing draft submission documents to sponsors before they are sent to Advisory Panels a uniform Agency policy.

B. Additional Proposals

The MBC proposes that the FDA introduce more self-reviewing and self-policing mechanisms that enhance transparency, such as uniform timetables and publication of performance results. In addition, as addressed below at Tab C ("Cooperation between FDA and Industry and Enhancement of the Roles of Industry Ombudsmen"), FDA should strive to increase its level of communication with industry through the implementation of FDAMA. As an initial measure, the MBC proposes that FDA enhance the roles of Industry Ombudsmen.



Massachusetts Biotechnology Council, Inc. **June 1998**

General Concerns Regarding Enactment of the Food and Drug Administration Modernization Act of 1997

Cooperation between the FDA and Industry and Enhancement of the Roles of Industry Ombudsmen

I. Background Information

Our industry fully recognizes that, without social acceptance, there will not be market acceptance of its products. Moreover, to succeed in the business of life science, especially given the finance pressures associated with contemporary health care, products must be safe, efficacious and, increasingly, cost-effective. There is full appreciation among the MBC's Member Companies that these standards must be realized, and there is willingness on the part of industry to work with FDA to accomplish nothing less.

Therefore, the MBC embraces the opportunity to cooperate constructively with the FDA to realize the overarching objective of FDAMA--the timely introduction of breakthrough health care products. Specifically, FDAMA mandates that FDA "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner . . . ." FDAMA, § 406(b) ("Mission"). The Agency is ordered to carry out this mission "in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products." FDAMA, § 406(b)(4).

II. Discussion Points

FDA should make an effort to continue the period of industry input now underway during the implementation of FDAMA. To achieve cooperation between industry and FDA, FDA should provide our industry with a meaningful venue through which we can communicate in a collective manner, on an ongoing basis, and with minimum susceptibility to recourse. The role of the Office of Chief Mediator and Ombudsman (Ombudsman Office) should be enhanced to serve as such a mechanism.

First, the Ombudsman Office should assume more of a proactive role--e.g., by organizing issue-identification forums that enable industry representatives to speak in a collective, less identifiable manner. In addition, the Ombudsman Office should revisit its strong preference for handling problems at the center level, and it should more readily exercise its agency-wide jurisdiction. Sponsors should have the option of immediately raising reviewer and center-specific issues directly with the Office and having their issues addressed at that level--i.e., once removed from the reviewer and center they are having problems with--without resistance.

Moreover, FDA should reconsider its policy of filing sponsor complaints about reviewers in those reviewers' personnel files and not making them otherwise available--i.e., available according to subject matter and in a collective manner. The Agency's current practice grossly impedes the ability of sponsors to research problems (both problems with individual reviewers and challenges to policies), and to present the strongest possible cases

for change to FDA. The result is a lost opportunity to improve the operations of the FDA, which translates into a detriment to patients who await breakthrough products.

CROSSFILE SHEET

This document has been cross-filed in the following dockets.

98D-0267/C3

98N-0222/C53

98D-0468/C5

98N-0339/C3