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Industry representatives also claim that FDA requires two or more well controlled studies to provide evidence of effectiveness for a drug or biologic when one study should suffice.

As to what constitutes an adequate demonstration of effectiveness for a new product, FDA has interpreted the FD&C act as requiring two or more well controlled studies. From a scientific perspective, what FDA seeks to have demonstrated is that a showing of effectiveness in one study can be replicated. While a second study may well be needed to replicate the results of the first study, it is also possible to replicate results within one large, well designed multicenter study.

The Genetech drug Pulmozyme was recently approved to treat cystic fibrosis on the basis of one multicenter study with features that provided elements of replication. Similarly, the drug timolol was approved to treat hypertension following a demonstration of improved survival in a single study involving three different patient groups in three different hospitals; and a multicenter double-blind placebo-controlled trial led to prompt approval of zidovudine for AIDS in 1987 when it was found that 16 deaths had occurred in the placebo group, as opposed to 1 death in the group receiving the drug.

THE CBER LOT RELEASE PROGRAM

BACKGROUND

Historically, biological products have been complex mixtures produced by living organisms, including vaccines, coagulation factors and other blood products and a variety of extracted materials, which have been impossible to define in precise molecular terms. Though genetic engineering and recent advances in analytical techniques have allowed much greater control by manufacturers over certain aspects of production, recombinant products are propagated in living systems and so are unavoidably heterogenous to some degree. Therefore, significant limitations remain in our ability to completely characterize most biological products.

PROPOSAL

The lot release program at CBER serves an appropriate role in the regulation of biological products which may vary in composition from heterogeneous mixtures to more highly characterized and well defined entities. Greater control by manufacturers over production of biologicals has allowed the Agency to reconsider the lot release requirements. In the future, CBER will not automatically require lot release with the approval of each new biological product license application without first considering the scientific and regulatory data which defines the extent of product characterization and the compliance history of the applicant. Following these considerations, the Director, CBER will determine when lot release should be required as well as the duration of time that any such requirement should be imposed.

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This interpretation will not require a change in the existing regulations governing lot release at 21 CFR 310.1 and 310.2.

Genentech, Inc.
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Genentech, Inc.

Memorandum

GOVERNMENT AFFAIRS

To: Chris Jennings
From: David Beier
Date: Monday, March 06, 1995
Subject: FDA Reform

Concept Paper: 2/27/95

FDA REGULATORY REFORM

A Proposal by the Biotechnology Industry Organization

SUMMARY:

Promotion of the public health, increased international competitiveness, and modernization of government regulation are paramount goals of Food and Drug Administration (FDA) reform. A renewed FDA can serve the needs of the patient community, general public, and stakeholders better by focusing greater effort on the timely approval of safe new drugs, biologics, and devices and less effort on unnecessary and marginal activities.

Redefinition of the FDA should proceed in two stages. First, short term changes in legislation and regulation that advance these goals should be pursued promptly, with vigor. Second, a longer term, more comprehensive set of goals should be advanced, debated and acted upon. Given the complexity, importance, and controversy of some of the longer term goals, we should not delay the achievement of a more modest set of accomplishments.

The short term proposals in this document will improve FDA efficiency by freeing up resources to focus more effort on analysis and approval of new therapies. The reforms are also aimed at improving physician access to relevant information about regulated products and removal of impediments to American businesses in the international marketplace.

THE PROBLEM

The Food and Drug Administration (FDA) is an important and powerful federal agency. The FDA -- by its own estimates -- regulates one quarter of the consumer products in the United States. The FDA currently has 9500 employees, a budget of \$975 million per year, and far

reaching regulatory responsibilities. Despite frequent reform recommendations, most legislative change over the past 20 years has resulted in an increase in the Agency's regulatory responsibilities. Virtually no Congressional attention has been given to updating FDA's authorizing statutes to address new technology. It is time to analyze FDA's mission and structure in order to improve the promotion of public health, reduce unnecessary regulation, and improve America's competitiveness.

The Biotechnology Industry Organization (BIO), representing over 580 companies and affiliated organizations, has reviewed the activities of the FDA and presents a preliminary report on short term action opportunities to improve the Agency. This report stems from certain problems our member companies and their customers, the patient communities, have experienced with current FDA regulation.

Delay in Moving Products from Discovery to Approval

The average time to move a product from bench to bedside in the 1970s was 5-7 years. Today the average time is 10-12 years. The increase in the cost of developing a new drug in the same period has risen from \$70 million to over \$359 million in 1980s. The cost of developing new products in the 1990s is likely to increase to \$500 million. During the past decade the total cost to develop a new drug has increased at an annual rate of more than 8% per year above the general rate of inflation.

The delay in approvals in the United States denies patients rapid access to needed therapies. Increased cost of development drives up the prices of the end products.

The drug lag is most easily demonstrated by the fact that between 1985-1993 only 27% of all new drugs were first approved in the United States. Moreover, for drugs with one or more years of foreign marketing experience prior to United States approval, the period of prior availability was about 6 years.

The consequence for patients is seen when looking at cancer therapies. Of the approximately 100 anticancer agents approved in the last 30 years, less than half were available in the United States (compared with over 60% in Japan and Germany). In the area of psychotropic drugs the delay in access is more dramatic. Over one-third of these agents approved in the past 30 years were available at least 6 years earlier outside the United States. Besides delaying the access of new drugs to American patients, the FDA indirectly creates additional costs to the health care system. In most cases, new drugs are the most cost effective means of treating the patient particularly when they reduce hospital stays or eliminate processes such as surgery or blood transfusions.

Despite efforts by the Agency to address the approval process of submitted applications through new regulations and more recently, through the use of user fees, much remains to be done. The cost and complexity of clinical trials (that is the work necessary to gather data prior to the submission of an approval application) has increased significantly. This cost of tests and related procedures per patient between 1989 and 1993 has gone up by 69%, 118%, and 51% for Phase I, II, and III trials respectively. This has been a significant contributor to the lengthening of the drug development process. Finally, the time between filing of an IND (seeking permission to conduct human clinical trials) and the submission of an approval application has gone from 2 and one half years in the 1960s to 6 years in the 1990s.

Excessive Regulation

The Food and Drug Administration has introduced many new regulations that are tangential to the fundamental mission of approving new therapeutic products.

Examples of excessive regulation include:

- Excessive regulation of the early clinical trial process, including the submission of INDs. Currently, over 60% of all Phase I INDs are filed by individual scientists and

academic health centers. These investigations rarely lead to commercial therapies and their consideration delays approval activities by FDA reviewers.

- ▶ Needless submission of advertising and promotional materials for prior FDA approval.
- ▶ Restrictions on export of unapproved products to countries that have approved them and review of foreign labels for approved products being exported.
- ▶ Requirement of prior FDA approval for minor manufacturing changes of well characterized biotechnology products, when prior approval is not required for traditional drugs.
- ▶ Requirement of an Establishment License in addition to a Product License for biotechnology products.
- ▶ Current regulations on lot release needlessly consume FDA resources, increase costs and may, in some instances delay patient access to biotechnology products.

Lack of Agency Focus

In some instances the FDA's mission of protecting the public is being pursued without a requisite recognition that it also plays an important role in the promotion of innovation and the prompt approval of new therapies needed by seriously ill patients.

Specific examples of the lack of focus include:

- ▶ Unfocused research activities by FDA employees. In some instances this research is not relevant to the Agency's mission of approving products. The research activity in some instances needs to be focused on product approval issues, such as the

development of surrogate endpoints that would expedite the development of important new therapies, and the expertise of outside experts should be more effectively -- and less expensively -- utilized.

- ▶ The FDA has in recent years devoted a disproportionate amount of its own resources pursuing relatively insignificant activities, including excessive regulation of the approvals of new supplements for drugs, label changes, and in some instances regulation of promotion and advertising.

Failure to Effectively Use Outside Resources

The FDA has not moved aggressively enough to implement the recommendations of the Edwards Commission on the use of outside reviewers. Agency efficiency would improve through the intelligent use of outside experts.

International Competition

Under current law, the FDA is forced into playing the role of international public health policeman by regulating the export of biotechnology products to other countries. No other industrialized nation imposes similar restrictions on exports. The limitations on drug exports cost American jobs, create an incentive to build new manufacturing facilities overseas, and put the FDA in a position of denying new products to countries whose own regulatory systems have approved them. To the extent that foreign countries approve and ask American firms to deliver biotechnology products, there should be a compelling, valid reason before the Federal government intervenes on behalf of foreign consumers.

Limitations on the Dissemination of Information Hurts Patients and Doctors

The Food and Drug Administration has limited the dissemination of relevant medical information from respected medical journals, textbooks and the proceedings of major medical and scientific societies. These limitations sometimes deprive the medical community of easier access to important medical information, hurt patients, and do not reasonably advance public health.

PROPOSED SOLUTION

BIO recommends initial steps to improving patient access to new therapies as a part of transforming and renewing the FDA. Promotion of the public health, increased international competitiveness, and prompt revision of regulations are paramount goals of renewing the Food and Drug Administration. A renewed FDA can serve the needs of the patient community, general public, and stakeholders by focusing its mission on promoting the timely approval of safe new drugs, biologics, and devices.

Transformation of the FDA should proceed in two stages. First, short term changes in legislation and regulations that advance these goals must be pursued with vigor. Second, a longer term, more comprehensive set of changes should be implemented. BIO will be pleased to work with the FDA, members of Congress, the Administration, patient groups, and physicians; on a longer term reform agenda for the FDA. Pursuit of the initial reforms outlined in this paper should compliment this effort by immediately improving access to new products and by providing better information about those products. Moreover, small companies, especially in the biotechnology drug and device industry, will materially benefit from the revision or removal of unneeded regulations, thereby nurturing their economic growth.

The short term proposals in this document will better focus FDA resources on the analysis and approval of new therapies. Although framed as a legislative proposal, some of the outlined goals may be achievable by reorienting FDA policy or through Agency rulemaking. Over a decade of exposure to FDA regulatory activities convinces us that, in several instances, these activities can be updated, limited or contracted to outside experts without any sacrifice whatsoever to the public health and safety. BIO proposes modifications to current requirements for product review, inspections, advertising, and export control that, in our view, will save the federal government money, transfer scarce FDA resources to product evaluation activities, reduce unnecessary and expensive regulation, and make important new therapies available to patients more rapidly.

Proposal

1. **PROBLEM:** The Center for Biologics Evaluation and Research (CBER), the Center for Drug Development Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) each review biotechnology products under different statutes and regulations. In many cases this results in inconsistent and inappropriate regulation. The Federal Food, Drug and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) both require long overdue amendment to reflect advances in new technology.

Although the requirements to demonstrate product safety and efficacy are the same, inconsistent policies and regulations among the Centers result in substantially different regulation of manufacturing processes. There no longer is any rationale for distinguishing by law between biological products and drugs with differing regulations predicated on statutory definitions. Rather, differences in regulation should be based on the character of the products being regulated. We thus propose consolidation of current biologics regulation under the PHS Act with those of the FD&C Act with differing requirements only where warranted, based upon individual product characteristics.

The authority to require an Establishment License Application (ELA) has been interpreted over the years by CBER to require approval of even the most minor changes in manufacturing of products made in facilities subject to an ELA. The resulting paperwork and delays are often costly, time consuming, and unnecessary. ELAs are an anachronism in today's world for most, if not all, biotechnology products. In addition, FDA has, on many occasions, required that material for pivotal clinical trials be produced at commercial scale requiring the construction of expensive facilities prior to product approval. In most instances, this requirement is outdated. Finally, the requirements for designating a "responsible head" who is solely responsible for handling correspondence with the FDA is outdated and highly restrictive in terms of delegating authority for product manufacturing and quality control.

SOLUTION: Modify current law to eliminate inconsistencies between how traditional chemical and biotechnology drugs are regulated where these inconsistencies have no rational scientific basis. These modifications should also provide clearer direction as to the circumstances under which manufacturing changes must be pre-approved by FDA.

- a. The authority under the PHS Act to require ELAs should be replaced by a new requirement, applicable to all drugs (including biologicals), that products be manufactured in accordance with good manufacturing practices and thereby apply the same regulations to biologics as currently applicable to drugs.
- b. Make it clear that responsibility for regulating in vitro diagnostic products vests solely with the CDRH. (This would result in the transfer of responsibility for blood test kits from CBER to CDRH).
- c. Human tissue intended for transplantation should be subject to standards that insure safety and not premarket review. Use of outside accrediting and standard setting bodies should be authorized and encouraged.

- d. FDA should be required to establish two sets of regulations concerning manufacturing changes. One set of regulations would apply to traditional chemical and biotechnology drugs which can be characterized adequately by physical and chemical methods. For these products, FDA should regulate the finished product and not the process by which it is manufactured. Another set of regulations would apply to products which cannot be so characterized, providing for regulation of process as well as product. Submissions describing manufacturing changes which require approval by FDA before they are implemented would be required only for changes specified by FDA that could substantially affect the safety or efficacy of the drug, similar to the way in which non-biological drugs currently are regulated.
- FDA should not require for a product that can be adequately characterized (and should rarely require for a product that cannot be adequately characterized) that a manufacturer build and operate a full scale commercial plant before completing clinical trials. In order to facilitate more rapid access to new products, FDA should accept clinical data from material produced at pilot scale rather than requiring additional clinical trials to be conducted on material produced at full scale.
 - Other manufacturing changes required to be submitted to FDA should be handled in a manner similar to current requirements relating to the submission of investigational new drug (IND) applications. Unless FDA objects to an IND within 30 days of acceptance for filing, the IND becomes effective. Similarly, a manufacturer's submission of a proposed manufacturing change will go into effect 30 days after the submission, unless FDA takes affirmative action for demonstrated cause to halt it.

- e. Changes not covered by subparagraph (d) would be submitted in a manufacturer's annual report.
- f. Lot release should not be required automatically for any drug. Whenever FDA has concerns about a particular product related to manufacturing or quality control it should conduct lot certification for 6-12 months, after which it shall authorize self-certification unless the safety and efficacy of the product cannot be assured without FDA's continuing review and product certification. Under the new law, FDA will be required to certify a reasonable number of commercial laboratories to conduct timely lot inspection and release.
- g. The requirement that a "responsible head" of a facility be identified should be eliminated.

Our proposal does *not* call for the combining of CBER and CDER, the two Centers that currently are responsible for the regulation of biological products and drugs. We regard reorganization in response to our proposed statutory changes to be the province of the Executive Branch.

2. **PROBLEM:** The approval of drugs and biologicals is unnecessarily costly and time consuming because full FDA resources are not oriented towards the review and approval of new drugs.

SOLUTION: While, in general, improvement of the drug approval process must be undertaken in conjunction with long term reform, several statutory changes can be made immediately:

- a. Committee report language should encourage FDA to the extent feasible and maintaining high standards of efficacy and safety to work with sponsors so that one pivotal clinical trial can serve as the basis for approval of breakthrough drugs.

- b. FDA should discontinue review of all Phase I INDs sponsored by an individual researcher or academic institution; approval of these Phase I studies should be the responsibility of Institutional Review Boards (IRBs) which will be individually certified by FDA or NIH for this purpose. Commercial sponsors of Phase I studies should have the option of proceeding either in this manner or of requesting FDA review. In addition to insuring informed consent and an appropriate benefit/risk relationship, IRBs certified to approve INDs for Phase I studies must undertake the new responsibility of insuring that the protocol has received appropriate scientific review. All sponsors of Phase I INDs should be required to notify FDA at the initiation of clinical trials and report to FDA any adverse events as a result of the trial.
- c. FDA should have 30 days to respond to new data regarding clinical holds or other IND amendments or supplements. Trials may proceed if FDA does not respond.
- d. Minutes of meetings between FDA and drug sponsors applicable to study design and size of clinical trials should be exchanged.
- e. Any research activities of the FDA must be narrowly focused and linked to the drug review process, such as the development of surrogate endpoints. FDA can conduct such research in collaboration with National Institutes of Health (NIH), academic health centers, industry and other scientific institutions. In addition, FDA should encourage exchanges of its scientists with academic health centers and industry.

A Scientific Review Board appointed by the Secretary of HHS, and consisting of members of the scientific community from academia, industry and government (other than FDA), should oversee the research activities of FDA.

3. **PROBLEM:** The biotechnology industry experiences significant loss of time and money due to lack of FDA's use of outside experts and laboratories to conduct certain activities.

SOLUTION: FDA should be required to contract with qualified experts to perform a significant number of the following activities:

- toxicology reviews
- environmental reviews
- validation of assays
- lot release (see point 1(f) above)

These activities would be paid for by FDA, as EPA does for pesticide and toxic substance review activities.

4. **PROBLEM:** Current export laws compromise the ability of pharmaceutical and biotechnology companies to compete effectively in the international marketplace. Unapproved drugs and biologicals not approved for sale in the United States may only be exported to 21 countries listed by statute that have approved them. In addition, current regulations require approved biologics and drugs to be exported only with labeling approved by FDA. Obviously, products to be shipped outside of the United States must have labeling approved by the government of the country to which the product is being exported, and these governments often have labeling requirements which are inconsistent with FDA regulations.

SOLUTION: The current restrictions on export of drugs or biological products not yet approved in the United States required in Sections 801(d) and 802 of the FD&C Act, should be replaced with a requirement that FDA authorize promptly a United States company, upon application, to export such products to any country that has licensed them for sale or testing. Unless the FDA takes affirmative action to prohibit export within 30 days, export approval shall be deemed to be granted. FDA should continue to require companies to report adverse events in foreign countries.

The proposed legislation would remove FDA jurisdiction over labeling of products intended for export.

5. **PROBLEM:** FDA has exerted authority over "labeling" and advertising in ways which make it difficult to provide factual information to the medical profession. Conflicts between FDA's policy and SEC regulations is a particularly important issue for biotechnology companies and other small publicly traded firms, where significant events in product development constitutes material information. Failure to keep the investment community informed about material developments exposes companies to shareholder lawsuits and puts corporate officers at risk of criminal prosecution. The FDA has no jurisdiction over such matter and should not attempt to exercise power in this area.

SOLUTION: Legislation should clarify current law by prohibiting the exercise of jurisdiction over advertising by FDA as follows:

- a. Under current FDA guidelines, companies are prohibited from providing reprints of peer-reviewed articles unless the articles comport in every way with the approved product labeling. For instance, they may describe a different dosage than that approved by FDA; they may not contain as detailed a discussion of side effects; or they may describe treatment of a different indication. Nevertheless, physicians rely on peer-reviewed articles and other reputable scientific publications as an important source of information about medical advances. Therefore, companies should be permitted to disseminate reprints of peer-reviewed articles and proceedings of scientific meetings to physicians, regardless of whether those publications contain information about unapproved drugs or unapproved uses of approved drugs. Under the new legislation, such articles and publications would not be subject to regulation as labeling.

- b. FDA jurisdiction over independent scientific and educational conferences which are not controlled by manufacturers or individuals who are employees of the manufacturers should be removed under the new law.
- c. FDA should be prohibited from requiring prior approval of sales and marketing literature.
- d. The category or type of information required to fulfill requirements of the Securities and Exchange Commission should be exempted from FDA regulation.
- e. FDA oversight of trademarks shall be eliminated.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

LRM NO: 3532

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2/15/96

LEGISLATIVE REFERRAL MEMORANDUM

Total Page(s): 26

TO: Legislative Liaison Officer - See Distribution below:

FROM: Janet FORSGREN *Janet R. Forsgren* Assistant Director for Legislative Reference

OMB CONTACT: Robert PELLICCI 395-4871

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SUBJECT: HHS Proposed Testimony on the promotion of unapproved uses of prescription drugs and medical devices.

DEADLINE: 10:00 a.m. Wednesday, February 21, 1996

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President.

Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.

COMMENTS: Hearing is before the Senate Labor and Human Resources Committee on Thursday, February 22nd. FDA Deputy Commissioner for Policy Bill Schultz is the Administration witness.

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FPA AK: off label uses

DRAFT

Kassebaum Hearing

INTRODUCTION

Madam Chairwoman and Members of the Committee. I appreciate the opportunity to testify on the important issue of promotion of unapproved uses of prescription drugs and medical devices.

My name is William B. Schultz. I am the Deputy Commissioner for Policy at the Food and Drug Administration. I am accompanied today by Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, Dr. Bruce Burlington, Director of FDA's Center for Devices and Radiological Health, [and. . .]

FDA SUPPORTS THE DISSEMINATION OF INFORMATION TO PHYSICIANS

Madam Chairwoman, I am here today to talk about uses that do not appear in a product's FDA-approved labeling and are not approved by the agency. Such uses commonly are referred to as "off label," "unapproved," "unlabeled," or "extra-label" uses. The Food and Drug Administration recognizes that, in certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice. FDA knows that there are important off-label uses of approved drugs. In this context, it is important that physicians have access to accurate information about drugs. But we also know that allowing the promotion of these kinds of uses can have negative public health consequences -- including exposing patients to unnecessary risks and destroying the incentive for companies to conduct the necessary research to demonstrate that products are safe and

effective for these uses. Striking the proper balance between the need to regulate the promotion of unapproved uses for drugs and devices and the need for reliable scientific data and information on unapproved uses of approved products is a difficult and controversial challenge.

FDA'S REGULATORY AUTHORITY

I would like to start today by explaining how, in passing and amending the Federal Food, Drug, and Cosmetic Act (FDC Act), Congress struck that balance and what, as a result of Congressional decisions, FDA can and cannot do with respect to off label uses.

The legislative history of the Federal Food, Drug, and Cosmetic Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling.

Generally, FDA does not prohibit the dissemination of information to health care professionals. Physicians access information about off label uses through compendia, journal articles, continuing medical education programs, symposia, and professional meetings. Physicians also have access to a number

of databases that provide information about off label uses. For example, the National Cancer Institute's Physician Data Query (PDQ) system is an excellent source for oncologists to obtain information about current oncologic therapies. The National Library of Medicine (NLM) offers a Medical Literature Analysis and Retrieval System (MEDLARS), which is a computerized system of databases and databanks pertinent to biomedical research and patient care. NLM currently offers free access to three databases relating to AIDS. FDA does not regulate a physician's access to any of these types of independent off label use information -- no matter how preliminary it may be. In addition, FDA does not prohibit a manufacturer from providing a physician information about off label uses if the physician requests that information. Recently, the Agency announced a proposed change to its policy with respect to the dissemination of reference textbooks. Drug companies may distribute independent reference text books even if they contain certain information about off label uses of approved drugs, as long as the textbooks do not have a significant focus on an off label use of the manufacturer supporting dissemination of the text. FDA recognizes that all of these sources of information can be very important to good medical practice.

Although the Federal Food, Drug, and Cosmetic Act does not permit FDA to regulate the practice of medicine, it specifically directs FDA to regulate the promotion of drugs and devices.

Promotional materials are false or misleading if they promote an unapproved use for the product; contain claims relating to the dosing, safety or effectiveness of the product that are inconsistent with the approved labeling; or if they lack a fair and balanced presentation of information, i.e., of benefits and risks. Although submission of an article for publication in a journal is not promotional, the use of such an article to sell a drug or device is promotional.

The Food and Drug Administration Performance and Accountability Act of 1995, S. 1447, abandons the current approach. It would permit drug and device companies to promote the sale of their products by distributing journal articles, textbook chapters, continuing medical education program materials, and compendial information relating to uses recognized for purposes of third party coverage or reimbursement that discuss off label uses. The bill also would permit drug companies to distribute summaries of journal articles, textbook chapters, CME program materials, or information relating to uses recognized for purposes of third party coverage or reimbursement. Device companies could distribute oral and written information about off label uses that are part of an "exchange" among health care practitioners, health care reimbursement officials, and the industry, that is exchanged for "educational or scientific purposes, or that is presented at CME programs, seminars, workshops, or demonstrations for devices.

We recognize that the purpose of the bill is to enhance dissemination of information and not to facilitate or encourage promotion of off label uses. But we strongly believe that if the bill is enacted, that will be its effect. Drug and device manufacturers market their products principally by sending sales representatives, referred to as detail men and women, out to talk one on one with physicians who might prescribe their products. A detailer's job is to convince those physicians to use and prescribe their products. They do this by providing information that purports to describe the usefulness of their products in the patient population. Written materials such as journal articles that discuss favorable studies of these products are powerful tools in the hands of a detailer. If the bill is enacted, drug and device companies will be free to use these materials to promote off label uses.

Pursuant to the bill, after a company receives FDA approval of a drug or device for one use, it would be permitted to promote that product, through these other means, for other uses. The material that companies could distribute often would be very preliminary. Companies could promote the use of a product even when the evidence merely suggests or can be interpreted as suggesting that a product may work for a specific use. Effectiveness would not have to be demonstrated. Thus, if drug X is approved for cancer patients, and there is some preliminary data that suggests it is beneficial for patients with crippling

arthritis, the drug's manufacturer would be permitted to promote the drug and encourage its use for arthritis on the basis of this preliminary or unsubstantiated data. This promotion would be permitted even though the data have not been reviewed by independent scientific FDA experts.

In addition, the clinical information that appears in the materials that the bill permits manufacturers to distribute has not been validated in any way. For example, neither peer reviewers nor textbook editors review the data underlying a study described in a journal article or textbook chapter. In fact, peer reviewers and editors do not even see that data.

FDA has serious concerns regarding the promotion of indications that have not been approved by the Agency. Because promotional activities of drug companies and others are substantially motivated by profit and market expansion, the widespread promotion of prescription drugs and devices for uses that have not been determined to be safe and effective could be detrimental to the health and safety of the public. Permitting companies to promote drugs and devices for off label uses could have a number of devastating consequences for the quality of medical care in this country.

PROBLEMS WITH PERMITTING PROMOTION OF OFF LABEL USES

The fundamental problem with permitting the promotion of off

label uses is that not all off label uses are safe and effective. The only way to know which ones are safe and effective is to collect and analyze the data supporting a finding of safety and efficacy. Because off label uses data has not been collected and analyzed, their promotion raises a number of serious concerns.

Undercutting the Efficacy Standard

Permitting the promotion of off label uses based on studies reported in journal articles or other texts that clearly are an inadequate basis for approval by FDA would undercut the efficacy standard.

A fundamental precept of drug and device regulation in this country is that these products must be proven safe and effective before they can be sold. The requirement that these products must be proven effective, on the basis of adequate and well-controlled clinical studies, was first adopted by Congress in 1962. Congress specifically added the concept of effectiveness to the definition of "new drug" in order to ensure that the efficacy requirement would apply not only to initial claims made for a drug, but also to claims made after the initial new drug application had been approved. 108 Cong. Rec. S22044-46 (daily ed. October 3, 1962); S. Rep. No. 1744, 87th Cong., 2d Sess. Part 2 at 267, 271 (1962) ("On what logical basis can one possibly argue that the initial claim for a drug . . . should be supported by "substantial evidence" but that successive claims . . . should

not be so supported?" 108 Cong. Rec. at S22045.)

The addition of the "efficacy standard" revolutionized drug development and approval, not only in the United States, but worldwide, as well. Essentially, a manufacturer cannot just say that a product works for a particular disease or condition, it must prove that the product works for that disease or condition. The only way manufacturers can prove efficacy is by submitting data from adequate and well-controlled clinical trials for evaluation by independent experts at FDA. Anecdotal reports and poorly controlled observations do not suffice because those kinds of reports may be wrong or may not be an adequate basis for conclusion. We know this because we have had experience with this type of information. Many drugs approved before 1962 turned out not to work when, after 1962, they had to be (and were) studied.

The solid foundation that is laid down by the efficacy standard is one of the main reasons that there is a strong sense of confidence in the drug products that are on the U.S. market today. Because the standard requires adequate and well-controlled clinical trials, once FDA made a determination of effectiveness, there can be a high degree of confidence that the drug will work. Thus, when a manufacturer claims that a product is safe and effective for a particular disease or condition, doctors can be confident that the product is in fact safe and

effective for that disease or condition. Patients, in turn, can have confidence in the quality of the products they are receiving.

Eliminating the efficacy requirement would be a major setback for the first-rate medical care that the health care system in this country provides. Consider some of the additional uses that FDA has approved -- for example, timolol for heart attack patients, taxol for breast cancer, and alpha interferon for hepatitis B. Without the requirement to submit clinical studies to prove that drugs are effective for their intended uses, it is far less likely that we would know that these drugs will work to decrease mortality in heart attack patients or to treat breast cancer and hepatitis B. In the absence of the efficacy requirement, the market will be filled with drugs that manufacturers claim work, but for which there is relatively little evidence.

Disincentive to Conduct Studies

One of the most serious consequences of allowing companies to freely promote off label uses is that companies would have no incentive to conduct the necessary scientific research and to present data to FDA to verify the safety and efficacy of those off label uses. In fact, because the agency might determine that the new use is not supported by the evidence, there would be an incentive to avoid FDA review. To use the example of the cancer

drug that may be useful for crippling arthritis, why would the drug company undergo the expense of actually studying whether the drug works for arthritis if it could promote the drug for arthritis based on preliminary evidence, particularly since a thorough study might fail to establish efficacy for arthritis?

In a world where off label uses can be widely promoted, manufacturers would have an incentive to do the minimal amount of studies necessary to obtain approval for the first, narrowest/easiest indication and then heavily promote the product for other broader (and possibly more speculative) uses. For example, interferon alpha was approved for use in hairy cell leukemia, of which there are approximately 300-400 cases per year. It subsequently was approved to treat hepatitis B, of which there are tens of thousands of cases per year. If S. 1477 was in effect, the manufacturer of interferon alpha could have sought approval for hairy cell leukemia and then just promoted for hepatitis B -- the much broader use. Interferon alpha is just one of many examples of a second use being significantly broader than the original use for which a drug was approved.

Under the approach taken in the bill, we might never learn whether interferon alpha actually works to treat hepatitis B -- yet the manufacturer could promote its use. This is precisely the scenario that Congress sought to prevent when it added the effectiveness requirement to the definition of a new drug. A

group of Senators, lead by Senator Kefauver, argued that unless the effectiveness requirement was added to the definition of drugs, "the expectation would be that the initial claim would tend to be quite limited, which of course, would expedite approval of the new drug application. Thereafter, 'the sky would be the limit' and extreme claims of any kind could be made," subject only to FDA's enforcement authority. 108 Cong. Rec. at S22046.

Because the incentive to conduct research on uses of drugs and devices will decrease, the end result will be that the dissemination of off label information pursuant to this bill will actually reduce the amount of information that health care providers receive about drugs and devices.

Safety Issues

Widespread promotion of unapproved uses also raises significant safety concerns. Even under the current law, which prohibits the promotion of off label uses, we know of a number of instances where physicians have used drugs for off label uses that have resulted in disastrous consequences.

For example, the drugs encainide and flecainide were approved for life-threatening and symptomatic arrhythmias, which are abnormal rhythms of the heart. In the late 1980's, physicians began to prescribe these two drugs for heart attack

victims who were experiencing ventricular premature complexes (VPCs), a type of asymptomatic or minimally symptomatic arrhythmia. (Asymptomatic arrhythmias are arrhythmias that can be detected by tests, but which the patients do not feel.) This off-label use, which was supported by published journal articles, was intended to prevent the well-documented increased mortality of heart attack victims who have a high level of VPCs by suppressing those VPCs. Ultimately, a National Institutes of Health study of the effectiveness of encainide and flecainide in these patients demonstrated that the risk of death was not decreased but was more than double in the patients receiving encainide and flecainide. If these unapproved uses had been heavily promoted by drug companies, it is estimated that thousands more unnecessary deaths would have occurred.

Another example relates to the widespread off label use of a class of drugs called calcium channel blockers (CCBs). These drugs are effective for patients suffering from angina, which is chest pain caused by insufficient oxygen to the heart muscle. CCBs have no established role in patients who have had a heart attack but have no symptoms. These patients do, however, benefit from beta-blockers, which are known to reduce mortality after heart attacks. Nevertheless, CCBs are widely used in this patient population. Because CCBs and beta-blockers cannot be used simultaneously, patients are receiving CCBs in lieu of clearly life-saving beta blockers. Countless lives are lost each

year because a drug of no known benefit is being used for an unapproved use in place of a drug with known value.

Yet another example of a case where the distribution of published articles on off-label use could have resulted in very serious harm to the public involves the Fentanyl (Duregistic) patch. Approved for use in chronic pain in patients requiring opioids, fentanyl was not approved for post-operative use because of concern that it would induce hypoventilation in people not yet titrated on opioids. A number of publications around the time of approval, however, described the drug as safe and effective for post-operative analgesia. After approval, reports to FDA and the literature documented life-threatening respiratory depression in post-operative patients given the patches. Extensive promotion of this off-label use could have been disastrous.

FDA is aware of a significant number of examples of journal articles describing off label uses that would be detrimental to a large number of patients if they were if heavily promoted. FDA fears that problems illustrated by these examples would be multiplied if manufacturers were given free rein to promote unapproved uses.

Unbalanced View

Another significant problem with permitting companies to promote unapproved uses by distributing the type of information

described in the bill is that physicians may not receive a balanced view of the available information. It is well documented that there is publication bias. Studies with favorable results have a greater likelihood to get published; studies with less favorable results less often get published. Moreover, even if less favorable results have been published, companies have no incentive to distribute articles, textbook chapters, or other information recommending against a particular use. Because the bill permits companies to distribute certain chapters of textbooks or mere summaries of journal articles, chapters, and CME materials, physicians may see only one side of an off label use story.

The current law governing promotion requires balance. Changing the law to allow the distribution of journal articles and other similar materials that discuss off label uses will allow drug detail men and women to provide materials that describe favorable study results of their product for a particular use, but without providing copies of materials that go the other way.

I would like to illustrate with an example. Human growth hormone currently is indicated for use only in children who are short because they lack sufficient growth hormone and children who are short because of kidney problems. Its use in children who are short, but have no growth hormone deficiency is an off

label use of uncertain value and safety. We identified four journal articles that discuss this off label use -- two more or less supported the off label use and two did not. If a physician receives information about this off label use from a detail person, it is possible that he or she will receive only the two favorable articles. On the other hand, if the physician were conducting his or her own research into the subject, he or she would likely locate both the pro and con articles. Given the approximately \$20,000 per year price tag of human growth hormone, the pain a child must endure because of multiple drug injections each week, and the potential adverse effects that growth hormone may cause (such as diabetes and possibly tumor growth), it is important that physicians see all pieces of the scientific puzzle.

By using this example, I am not targeting a specific drug or drug company. I am merely trying to illustrate what the bill would permit and why FDA has serious concerns.

What makes this situation even more troubling is that when we have evidence that a particular use is unsafe or ineffective, we believe that federal trade secret laws bar us from disseminating that information. The same trade secret laws bar me from providing you with specific examples of this. What I can tell you, however, is that there are off label uses about which positive studies appear in the literature and negative

information is contained in our files, and we are unable to use that information to ensure that the medical community has all of the available facts on which to base treatment decisions.

Even under current law, physicians have access to positive articles about off label uses and FDA is unable to counter those positive articles with any negative information that might be in our files. However, under current law, company detail men and women cannot use those articles to promote potentially dangerous off label uses.

The Bill's Requirements Are Not Substitutes for FDA Review

The bill imposes very few requirements on the off label use information that companies could disseminate. Basically, the unapproved use must appear in a peer reviewed journal article, a chapter from a recognized text, text from an approved CME program, information relating to a use recognized under Federal law for purposes of third party coverage or reimbursement, or a summary of one of the above. For devices, the information may also be from oral and written information that is part of an "exchange" among health care practitioners, health care reimbursement officials, and the industry, is exchanged for educational or scientific purposes, or is presented at CME programs, seminars, workshops, or demonstrations. None of these sources has procedures that confirm the validity of the data and information contained therein.

The purpose of the "peer-review" process, for example, is to determine if an article is worthy of publication. At best, peer review ensures that the reader is provided with enough detail and clarity to make judgements about the strengths and weaknesses of the study. However, there are no generally accepted standards for what constitutes "peer review." Essentially, anyone can establish a "peer-review" journal; the rigor of the review varies considerably. Regardless of the rigor, there are severe limitations inherent in the peer-review process that make it inappropriate to rely solely on a peer-reviewed journal article for efficacy determinations. For example, peer-reviewers do not have access to the underlying data. The peer-reviewers must rely on the data and facts as they are presented by the author. FDA, on the other hand, does have access to the data and can verify the statistical outcomes and conclusions of a study. Moreover, peer-reviewers do not necessarily have the time or the expertise in all aspects of the subject matter to adequately review the information. In fact, a survey of the literature reveals that a peer-reviewer spends on average less than three hours reviewing a prospective article. The peer-review process cannot guarantee the correctness, authenticity, or clinical importance of the article, nor can it detect fraudulent or flawed research.

The data and information supporting off label use that appear in reference textbook chapters, CME materials, and

materials related to third party coverage and reimbursement are even less likely to be validated than that in peer reviewed journals. In fact, we have no reason to believe that such data have been reviewed or validated at all. Textbook editors do not review the data underlying information about off label uses that appear in those books. The recognition of suggested uses in texts or treatment guidelines for purposes of third-party reimbursement serve different societal purposes. The decision to include such uses is not based on the standards used by FDA to substantiate safety and efficacy. FDA has serious concerns about a provision that allows companies to use these types of unproven/unvalidated information for promotional purposes.

There are many instances when uncontrolled studies have supported a use and subsequent well-controlled studies have failed to show effectiveness. Moreover, the literature is laden with studies that report preliminary findings -- e.g., studies that involve a small number of patients and case reports. Although the studies or reports may be scientifically accurate, they are not sufficient to show safety and efficacy. Thus, companies should not be allowed to use these less rigorous studies to promote off label uses of approved products.

GETTING SUPPORTED OFF LABEL USES ON THE LABEL

As you know, a drug is approved for its initial indications

via a New Drug Application, which includes data on the drug's safety and efficacy. A subsequent indication is added via a Supplemental New Drug Application, which usually needs to present only efficacy information to support that new use. After review and approval by FDA, the new use is added to the approved labeling and can be promoted by the drug's manufacturer.

There are several good reasons for drug companies to submit these "efficacy supplements":

- Approval usually ensures that third-party payers will reimburse for the use, as insurance companies virtually always pay for approved uses of drugs and devices.
- As health maintenance organizations continue to grow in size and number, a sponsor's ability to get their drug included in the HMO's drug formulary will be significantly enhanced.
- The physician, via the label, is given more complete information about the drug's uses, contraindications, adverse effects, and other important information about the manufacturer's product.
- Drug companies can present the FDA findings to drug approval bodies in other countries, thus enhancing their ability to gain approval (and reimbursement) for uses in other markets.

- And, of course, the manufacturer can promote the use, whether through the use of journal articles or other means.

Unfortunately, in many instances these incentives have been insufficient to persuade drug sponsors to submit efficacy supplements. There appear to be two reasons for their reluctance. First, they fear they will be expected to spend millions of additional dollars conducting new clinical studies to convince FDA reviewers that the new use should be approved. And second, they have often complained that efficacy supplements are given low priority by FDA, resulting in delays of years in getting new indications approved. These concerns -- or at least the perception -- have been valid in the past, and we at FDA must address them.

We have been working for months on ideas for encouraging and expediting supplements and for otherwise addressing the industry concerns. We're doing a number of things and have several ideas for additional progress in this area. Let me summarize them for you:

Expediting Review of Efficacy Supplements

As you know from yesterday's testimony, the Prescription Drug User Fee Act of 1992 (PDUFA) is helping resolve the problem of timely reviews for drugs. Under PDUFA, by 1997, the agency will make approval decisions on all standard new drug

applications (NDAs) within 12 months and within 6 months for priority drugs. These time frames apply to efficacy supplements as well. The approval times for NDAs and supplemental NDAs have decreased significantly, and the backlog of pending applications has also decreased markedly. In fact, for NDAs and supplemental NDAs, the agency has exceeded the interim goals established by Congress. For applications submitted in 1994, the agency has met its PDUFA goals for 96% of the NDAs and 73% of supplemental NDAs. [The interim goal for NDAs and supplements was 55%.] With adequate resources, we are confident that we can make the same progress for medical devices.

We should be able to exceed the PDUFA targets, however. I believe we should try to reduce the 6-12 month timeframes. To do so, we'll need to give supplements a greater priority than they have had in the past, and we're committed to that.

Less Data is Needed Than Commonly Believed

In addition to assuring companies that we can and will expedite their supplemental applications, we also need to address the industry perception that many efficacy supplements do not warrant the expense associated with getting them approved. Companies fear that they must conduct multiple and expensive new clinical trials and collect and analyze thousands of pages of medical data, with no assurances of approval. We need to better explain that in the vast majority of cases this is just not so.

Some off label uses could be approved by FDA if the sponsor would simply compile the existing literature and submit it to us. Others may need only limited new data. In any event, because FDA has already learned much about the drug's actions and effects in humans from the original application, the data required for second and subsequent indications is often far less than the original. It is, in sum Madam Chairwoman, a much simpler process than generally believed and we must convince sponsors of that. To that end, we intend to draft a new policy statement articulating the data needs of the agency for efficacy supplements.

Pediatric and Geriatric Labeling

We are already demonstrating how limited data can get more uses on the label in two important treatment areas. We have recently promulgated new regulations that provide for pediatric uses to be included on the approved labeling without new clinical data. For those indications, drug firms can take existing literature studies, extrapolate the data to children and get those uses on the label with relative ease. The only new data that will ordinarily be needed are information about the drugs course throughout the body (e.g., blood and tissue levels) that will allow the proper dosage to be established for children. Similar regulations have been proposed for geriatric uses. We expect those proposals to be finalized this year.

Seek Out the Most Appropriate Off-Label Uses

As I said earlier, many off label uses are quite appropriate, and some may even be the treatment of choice. Although off label use is seen in all medical specialties, it seems to be most widespread in certain areas, such as oncology and pediatrics. Beginning with those specialties, we will work with practitioners and their specialty associations to identify the off-label uses that are most appropriate. We will then present those findings to the sponsors of those drugs and urge them to work with us to get the indications on the label. In many, if not most, cases that will entail only the compilation of existing information, not the design and conduct of new clinical studies. We have not done enough to reach out to the medical profession and to drug sponsors on this issue, but we believe we can get the majority of the most appropriate current off label uses on the label through this process.

The best way to get information to physicians about the best of the drug and device armamentarium, Madam Chairwoman, is to get it on the product's label. Our collective goal ought to be to get this done.

Our confidence in drug and device therapy has been built on the recognized rigor of FDA's approval process. It is important that we not change a system that has the respect and



confidence of the health care community and the public. FDA recognizes that there are important lifesaving off label uses. FDA believes, however, that the best way to address any concerns that the information about those uses is not reaching medical practitioners is to get those uses onto the label.




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NUMBER OF PAGES W/O COVER: 19

COMMENTS: *Biologics info.*

Sent to Greg Simon 10/27/95 1230

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INTRODUCTION

In March 1995, the President announced a series of regulatory reform initiatives aimed at reducing the burden of FDA regulations on the drug and device industries without sacrificing any of the health and safety protections that the American people rightly expect for these products. The report, Reinventing Drug and Medical Device Regulations, issued by Vice President Gore's National Performance review, announced initiatives that will streamline the regulation of drugs and medical devices.

Today's report focuses on FDA's efforts to reform the regulation of biotech drugs used for therapy. The changes outlined in this report represent the most significant overhaul of regulation of biotech drugs ever attempted by the agency. FDA will in essence harmonize its regulation of biotech drugs that qualify as "well-characterized" between the two product centers of the agency that are responsible for assuring their safety and effectiveness. According to the biotechnology industry, these changes will save companies millions of dollars and cut drug development time by months. At the same time, the agency believes that these modifications will in no way diminish the

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agency's ability to review and ensure the safety and effectiveness of biotech drugs.

As described in greater detail in the body of the report, for well-characterized, therapeutic biotechnology-derived drugs, which include most biotech drugs, FDA will

- eliminate its existing requirement that manufacturing plants be licensed
- eliminate the existing requirement that test results for each individual lot of these biotech drugs be submitted to the agency after the product has been approved by the agency;
- will replace the 21 different applications that it currently has for biotech drugs, blood, vaccines and other drugs with a single application.

These and other initiatives described in this report will greatly streamline the regulation of biotech drugs, bring the requirements up to date with modern scientific understanding and manufacturing, facilitate the development and marketing of new biotech drugs, and enable the agency to continue to assure the safety and effectiveness of new biotech drugs brought to market.

Background

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FDA has two operating components that regulate drugs, the Center for Biologics Evaluation and Research (CBER) regulates blood, vaccines, and most drugs derived from microorganisms under the Public Health Service Act. The Center for Drug Evaluation and Research (CDER) regulates all other drugs under the Federal Food, Drug, and Cosmetic Act.

The drugs regulated by CBER are subject to additional statutory requirements over and above those required for all other drugs. Thus, for statutory reasons, as well as for other historical reasons, the two Centers have approached the regulation of biotech drugs somewhat differently. For example, because CBER is responsible for regulating products derived from living organisms under the authority of the Public Health Service Act, it requires two separate licenses for every product that it regulates: (1) a product license; and (2) a separate establishment license for each plant in which the product is manufactured. CBER also imposes lot release requirements on the products that it regulates under which it must certify the purity and stability of each batch of the drug prior to the time it is sold to the public.

The agency is now proposing to harmonize the

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requirements of the two Centers for therapeutic drugs that qualify as "well-characterized," which includes most biotech drugs.

DRAFT**FDA's Proposals for Reform****Elimination of the Requirement for an Establishment License Application for Most Biotech Drugs**

Background: Section 351 of the Public Health Service Act, which is administered by the Center for Biologics Evaluation and Research (CBER), requires that biologics be manufactured in establishments holding a license. In addition to the product application, which both the Center for Drug Evaluation and Research (CDER) and CBER require, CBER currently requires manufacturers of all biologics, including the biotech drugs it regulates, to obtain approval of a separate establishment license application for each facility in which a biologic is to be manufactured. According to companies that manufacture biotech drugs, complying with this requirement can cost millions of dollars and delay their submission of an application to the agency by several months. Thus, the establishment license requirement places a significant burden on the industry to produce them and the agency to review them.

Technical advances over the last 15 years have greatly increased scientists' ability to control the manufacture of many biotech drugs. After over a decade

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of experience with these drugs, the agency has found that it can review the safety, purity, potency and effectiveness of most biotech drugs regulated by CBER without requiring an establishment license.

Proposal: CBER will eliminate the requirement for submission and approval of establishment license applications for therapeutic biotech drugs that are "well-characterized." In place of the establishment license application, CBER will rely on good manufacturing practice inspections and a new chemistry, manufacturing, and controls section of a newly revised product license application, the format and content of which will be harmonized with a slightly revised new drug application for well-characterized biotech drugs that CDER regulates. (The revision will consist of the addition of a simple one page floor plan sufficient to visualize the production of the drug, but not requiring a detailed description of equipment placement.) Both CDER and CBER also will use the same guidance documents.

The harmonization across Centers of the chemistry, manufacturing, and controls format and content will also reduce the amount of information companies will need to provide in the product license application. In

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many instances, manufacturing information will not be submitted to the agency but will be reviewed at the manufacturing facility during good manufacturing practice inspections.

Pre-approval inspections for biotech drugs regulated by CBER will be done jointly by headquarters and field staff. These inspections will be comparable to those currently conducted by CDER for the biotech drugs they regulate. CBER will train its scientists and inspectors in conjunction with CDER personnel to ensure that inspection procedures for biotech drugs will be consistent across Centers.

As described in the National Performance Review's report on Reinventing Drug and Medical Device Regulations, CBER has already committed to reducing requirements for preapproval of manufacturing and site changes and is completing a proposed rule to that effect. Under this proposal, manufacturing and site change requirements for biotech drugs regulated by CBER will be harmonized with the requirements of CDER, and the proposed rule will reflect that.

To implement this proposal, the agency will adopt an interim definition of "well-characterized" drugs,

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limited to drugs used for therapeutic purposes. The agency anticipates that most therapeutic biotech drugs regulated by CBER will fall within this definition and therefore will be exempt from the requirement to submit and have approved an establishment license application. The agency is also sponsoring a public scientific workshop December 11 - 13 of this year, during which the participants will attempt to refine the agency's interim definition of well-characterized biotechnology-derived biologic drugs that will be eligible for these streamlining efforts.

The agency further anticipates that additional product classes, such as recombinant vaccines, may be encompassed by the definition to be crafted at the workshop.

FDA believes that these changes in regulatory procedures and requirements will not diminish the agency's ability to continue to ensure the safety, purity, potency and effectiveness of biotech drugs. This is because with in-process control and validation, the identity of the drugs to which the changes apply can be determined, their purity can be controlled and quantified, their activity and quantity can be measured, and both the manufacture and the end product

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release specifications can be validated. The FDA will apply current good manufacturing practice standards to these drugs in order to ensure their quality.

Impact: Companies developing and manufacturing most therapeutic biotech drugs regulated by CBER will no longer have to prepare establishment license applications and submit them to the agency for approval. The requirements of the product license application will also be reduced. These proposed changes will get these drugs to market faster and will enable companies to focus more resources on developing drugs and ensuring that they are manufactured appropriately, and less resources on documenting on paper how they are doing so. This will especially benefit small biotechnology companies that do not have experience preparing establishment and product license applications. The establishment license application requirement adds substantially to the cost of getting a biotech drug approved by CBER, partly because of the work involved in preparing and getting the license approved, and partly because it could entail building and operating a manufacturing facility long before the drug may be produced and sold.

These proposed changes also will remove significant

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obstacles to a company's ability to contract out manufacture of its drugs. These proposals will eliminate the requirement that each separate contract facility had to obtain its own establishment license. Instead, each biotech drug will be covered by only one marketing application, regardless of how many separate companies are involved in its manufacture.

Implementation and Timeline: Within 30 days, the agency will publish a proposed rule under which establishments manufacturing "well-characterized biotechnology-derived biologic drugs" would be deemed to have an establishment license if they were in compliance with current good manufacturing practice requirements. The proposal will include an interim definition of "well-characterized biotechnology-derived biologic drugs," and will allow 30 days for comment. The agency will publish a final rule 30 days after the close of the comment period.

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**Elimination of Lot Release Requirements
for Biotech Drugs**

Background: Biologics have traditionally been complex mixtures of substances produced from living organisms, including vaccines, products made from human or animal blood, and products made from a variety of materials extracted from living organisms that have been difficult to define by precise tests. Because of the inherent variability of these products, each individual lot of most biologics is subject to evaluation and testing by FDA before being released by the agency for marketing by a company.

Historically, the lot release requirement has served a very important role in the regulation of biological drugs and has prevented the release of unacceptable lots. Currently, greater control by manufacturers over the production of biotech drugs, and recent advances in analytical techniques, have enabled companies to produce consistent lots of biologics. For well-characterized therapeutic biotech drugs, the agency has found that once companies have demonstrated their ability to consistently produce acceptable lots, and have procedures in place that will prevent the release of unacceptable lots, there is no significant value

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added by requiring FDA to verify that each manufactured lot is acceptable for release.

Proposal and Justification: Once a well-characterized therapeutic biotech drug has been licensed for marketing, it will not be subject to lot release by FDA under normal circumstances. Instead, the agency will require companies as a condition of approval to demonstrate that they have produced 3 consecutive acceptable lots from 2 different batches, and after approval, to maintain records of their lot release test procedures and results.

Impact: The elimination of the lot release requirement for these post-approval biotech drugs regulated by CBER will result in a significant savings of time and resources for both the industry and the agency. There will be no significant additional risk to public health because these drugs do not raise manufacturing concerns warranting direct agency participation in quality assurance procedures. Additionally, the agency will monitor companies' compliance with the requirement that they assay each lot and only release acceptable lots.

Implementation and Timeline: The agency will immediately begin sending letters to affected companies

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advising them of the change in requirements. Within the next 30 days, the agency will publish a notice describing the elimination of FDA approval of lot release for well-characterized therapeutic biotech drugs.

DRAFT**HARMONIZED APPLICATION FORMAT FOR ALL DRUGS AND
BIOLOGICS**

Background: The Center for Biologics Evaluation and Research (CBER) currently uses 19 different product license application forms, and a separate establishment license application form. In addition, the Center for Drug Evaluation and Research has a separate new drug application form. This is very confusing for the industry and does not allow for a standard format for all biologics license applications, nor allow for the standardization of product applications for drugs and biologics.

Proposal and Justification: The agency proposes to consolidate the 21 different drug application forms into one. The harmonized form will contain a technical section on the establishment, which will be applicable only to those biologics for which establishment application review will continue to be necessary. The agency also intends to include some elements from the European format in order to facilitate international harmonization of applications. CBER also will revise its requirements regarding a "Responsible Head," allowing companies to divide management responsibility

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among appropriate regulatory, medical or manufacturing staff, consistent with current realities. Currently, CBER requires that there be a single "Responsible Head" who is to represent the manufacturer in all matters with the FDA.

In addition to a harmonized application form, the technical requirements and guidance documents will be the same across the agency for well-characterized therapeutic biotech drugs, regardless of which Center regulates them.

Impact: Companies will be able to provide consistent information and higher quality submissions. Time to prepare applications will be reduced because requirements will be clearly indicated.

The Center for Biologics will reduce 21 applications to 1 application and will enhance international harmonization. The standard format should facilitate easier review by FDA staff and can be used as a basis for electronic submissions. The ability to contract out will be the same for drugs and biologics across the agency.

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Implementation and Timeline: FDA intends to publish a revised format within 6 months. CBER will make available a draft form for product license applications for well-characterized biotech drugs within 60 days. CBER intends to publish a proposal to revise the regulation regarding "Responsible Heads" within 9 months.

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**ELIMINATION OF THE PRE-APPROVAL REQUIREMENT
FOR PROMOTIONAL LABELING**

Background: The Center for Biologics Evaluation and Research (CBER) currently requires pre-approval of promotional labeling prior to launch of a product and for 120 days following approval of a new product. This is inconsistent with what is required by the Center for Drug Evaluation and Research, which requires companies to send such information to the agency at the time that the company disseminates it.

Proposal and Justification: The Center for Biologics Evaluation and Research will revoke its current requirements that labeling in connection with the launch of a new product be approved.

Impact: Industry will no longer need to await approval of promotional labeling prior to disseminating it. Agency resources will be freed up to accomplish other review activities.

Implementation and Timeline: Effective immediately, the agency will no longer require preapproval of promotional labeling. FDA will publish a proposed regulation and a guidance document within 6 months.

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**AGENCY RESPONSES TO DATA
SUBMITTED REGARDING CLINICAL HOLDS**

Background: Companies or individuals that intend to study investigational drugs or biologics in humans must first submit an investigational new drug (IND) application to the agency. They may proceed with the study 30 days after the agency receives the application, unless FDA puts the study on clinical hold. A clinical hold is a directive issued by FDA that prevents the clinical study from proceeding. Thus, a researcher or company intending to begin testing a new biologic in humans, or in the process of testing a new biologic in humans, may not begin or continue the study until FDA releases the clinical hold. Currently, FDA has no internal requirements regarding how much time it may take to evaluate data submitted by the sponsor in response to the clinical hold. While the agency has generally responded in a timely manner, sponsors would like the predictability engendered by an agency commitment to respond within a specified time frame.

Proposal and Justification: FDA will commit itself to review and respond to data submitted in response to a clinical hold within 30 days of receipt of the

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submission. Absent a response from FDA within that time frame, the investigation may proceed. FDA believes that such a time frame will meet the needs of sponsors, and is within the resource capabilities of the agency.

Impact: The proposed change will prevent delays in agency review of data submitted in response to a clinical hold on an IND, and thus prevent unnecessary delays in the start or continuation of clinical studies.

Implementation and Timeline: FDA intends to publish within 6 months a guidance document establishing new procedures for reviewing data submitted in response to clinical holds on INDs.