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PRESIDENT BILL CLINTON
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JUNE 1995

*Reinventing
the Regulation of*

H U M A N
T I S S U E



PRESIDENT BILL CLINTON
VICE PRESIDENT AL GORE

FEBRUARY 1997

**REINVENTING
THE REGULATION
OF
HUMAN TISSUE**

**President Bill Clinton
Vice President Al Gore**

National Performance Review

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EXECUTIVE SUMMARY

The Food and Drug Administration's sixth "Reinventing Government" report, produced in conjunction with the Vice President's National Performance Review¹, focuses on the increasing use of human cellular and tissue-based products, and proposes a new approach to their regulation.

Tissues have long been transplanted in medicine for widespread uses—such as skin replacement after severe burns, tendons and ligaments to repair injuries, heart valves to replace defective ones, corneas to restore eyesight, and the use of human semen and implantation of eggs to help infertile couples start a family. In recent years, scientists have developed new techniques, many derived from biotechnology, that enhance and expand the use of human cells and tissues as therapeutic products. These new techniques hold the promise of providing therapies for cancer, AIDS, Parkinson's disease, hemophilia, anemia, diabetes, and other serious conditions.

Although these products are often the result of the newest technologies, the concepts and procedures under which they are regulated were developed many years ago, and sometimes are ill-suited for their purpose. To remedy this shortcoming, FDA—after consultation with the involved industries—has designed a new regulatory framework for cells and tissues that would protect the public health without imposing unnecessary government oversight.

¹ Previous reports include: "Reinventing Drugs and Medical Device Regulations" (issued April 1995); "Reinventing the Regulation of Drugs Made from Biotechnology" (issued in November 1995); "Reinventing the Regulation of Food" (issued January 1996); "Reinventing the Regulation of Cancer Drugs" (issued March 1996); and "Reinventing the Regulation of Animal Drugs" (issued May 1996).

This new framework would provide a tiered approach to cell and tissue regulation. Regulation would focus on three general areas: 1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; 2) preventing improper handling or processing that might contaminate or damage tissues; and 3) ensuring that clinical safety and effectiveness are demonstrated for tissues that are highly processed, are used for other than their normal purposes, are combined with non-tissue components, or (in many but not all cases) are used for metabolic purposes (i.e., for systemic, therapeutic purposes).

The tiered approach will impose regulation only to the extent necessary to protect public health, with little or no regulation for some products and with increasing degrees of oversight as the potential risk increases. In summary, tissues transplanted within a patient's body during a single surgical procedure would have no regulatory requirements. Tissues transplanted from one person to another for their normal functions without undergoing extensive processing would be subject to infectious disease screening and testing, and to requirements for good handling procedures, but would not need FDA review or marketing approval. Thus, most processors of conventional and reproductive tissues would not be required to submit information about their products to FDA or seek the agency's permission to market those products. The agency would require premarket approval for tissues that were processed extensively, combined with non-tissue components, or were to be used for purposes other than their normal functions. And FDA would in many cases require premarket approval for "metabolic" tissues (tissues that have a systemic, therapeutic effect on the body). Finally, the agency would require that all tissue processing facilities register with the agency and list their products (via a simple electronic system); and all labeling and promotion of the products would need to be clear, accurate, balanced, and non-misleading.

This new system would provide a rational, comprehensive and comprehensible framework under which tissue processors could develop and market their products. It would ensure that innovation and product development in this rapidly growing medical field could proceed unhindered by unnecessary regulation. At the same time, it would provide physicians and patients with the assurance of safety that the public has come to expect from drugs, biologics, medical devices, and other medical products overseen by the FDA.

A NEW REGULATORY FRAMEWORK

Introduction

The term “tissues” covers a wide range of products used for many medical purposes. In the past, most human tissue used in medicine was comprised of such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, and semen and ova implanted for reproductive purposes. Three years ago, FDA started requiring that conventional non-reproductive tissues be tested for HIV and hepatitis, and that their donors be screened for risk of infection. FDA did not impose any requirements on reproductive tissues at that time.

In recent years, scientists have developed innovative methods of manipulating and using human cells and tissues for therapeutic purposes. For example, in somatic cell therapy, scientists are studying how to manipulate and use human cells to treat viral infections, Parkinson’s disease, diabetes, HIV infection (AIDS), and other diseases and conditions. Other tissue research includes the treatment of diseases and medical conditions by using blood from the placental/umbilical cord, and by using processed structural cells and tissues.

Background

The FDA has formulated a comprehensive approach (summarized in the attached table) to the regulation of human cellular and tissue-based products.² This approach, which could be put in place with new regulations but without change to existing law, would provide a more appropriate oversight for the wide spectrum of cellular and tissue-based products that are now marketed or envisioned for the future. It would maintain or improve protection of the public and increase public confidence in these new technologies, while permitting significant innovation to go forward unfettered by unnecessary regulatory requirements.

Cellular and tissue-based products and their potential uses are too diverse to be appropriately covered by a single set of regulatory requirements. In an effort to develop a comprehensive scheme that would treat like products alike—but that would establish regulatory distinctions among cellular and tissue-based products when necessary—the agency identified the principal public health concerns and attendant regulatory issues associated with the use of these products. Stated as questions, these five overarching public health and regulatory concerns are:

- 1) How can the transmission of communicable disease be prevented?
- 2) What processing controls are necessary to prevent contamination of cells and tissues and to preserve their integrity and function so that they can be safely and effectively used?
- 3) How can clinical safety and effectiveness be assured?
- 4) What labeling is necessary, and what kind of promotion is permissible, for proper use of the product?

² The approach does not encompass whole organs or minimally-manipulated bone marrow (both of which are regulated by the Health Resources and Services Administration), or transfusable blood products (e.g., whole blood, red blood cells, platelets, and plasma), which FDA already comprehensively regulates. The approach also does not encompass other FDA-regulated tissue-related products, such as tissues derived from animals, products used in the propagation of cells or tissues, or products that are secreted by or extracted from cells or tissues (such as human milk, collagen, or growth factors).

5) How can FDA best monitor and communicate with the cell and tissue industry?

Proposal

With these concerns in mind, FDA differentiated cells and tissues and their uses by their risk relative to each concern, so as to enable the agency to provide only that level of oversight relevant to each of the individual areas of concern. Thus, under the plan, tissues would be regulated with a tiered approach based on risk. For example:

- FDA would not regulate cells and tissues removed from and transplanted into the same person in a single surgical procedure.
- FDA would subject tissues used for conventional purposes, such as to repair injuries, replace damaged or defective tissues, or overcome infertility, to limited oversight as long as they were only minimally processed and were used for their normal functions. The oversight would be aimed at ensuring that the tissues were handled properly and were not infectious. Other than facility registration, product listing, and reporting of any adverse events, the agency would require no submissions for most conventional and reproductive tissues used for their normal functions.
- The agency would require that all tissues (except when used in the patient from whom it was obtained in a single surgical procedure) be handled according to "good tissue practices" aimed at preventing contamination and preserving integrity and function. Additionally, the agency would prescribe procedures for testing the tissue for infectious agents and for questioning (screening) the donor about potential exposure to disease agents.
- For tissue to be used in the same person from whom it was obtained, or in a sexually intimate partner of a reproductive-tissue donor, the agency would recommend, but not require, that such screening and testing procedures be followed. While the agency would not get involved in the decision as to whether the tissue should be used, the agency would require that the prospective recipient be informed as to whether the recommended procedures were or were not performed, and of any results obtained. Additionally, for the

protection of health care workers, the agency would require that tissues be labeled according to whether or not they posed a potential biohazard.

- For tissue transplanted from one person to another (other than reproductive tissues between sexually intimate partners) the agency would require infectious disease screening and testing.
- FDA would require approval of human testing, and premarketing approval, based on a demonstration of safety and effectiveness, for tissues and cells processed such that their biological or functional characteristics may have been altered (or were intentionally altered), used to perform other than their normal functions, used for metabolic purposes (except when used between close blood relatives or in the person from whom the tissue was obtained), or combined with devices, drugs or other biologics. Technologies such as somatic cell therapy and gene therapy would fall into this category, as would stem cell therapy in patients not closely related to the cell donor.

Impact

This regulatory plan would establish a sensible, efficient, and comprehensive mechanism for classifying and regulating human cell and tissue products according to the potential risk they pose to human health. This plan would prevent pitfalls inherent in addressing each type of product separately under existing rules.

Under the plan, all facilities working with human cells or tissues would be required to register with the agency, and list their products, after the agency had in place a simple electronic system for such registration and listing. Thus, this new requirement would be of minimal burden to those affected. Additionally, the agency would minimize submissions by not requiring individuals or companies to submit information concerning communicable disease screening and testing, except in specified circumstances.

As a result, sponsors of lower-risk tissues (e.g., minimally processed conventional tissues for replacement purposes and minimally processed reproductive tissues) would not need to submit reports to FDA except for cases of adverse effect on a tissue recipient. The same minimal

requirements would also apply to minimally processed tissues used for their normal metabolic purposes in close relatives of the tissue donor. Sponsors of higher-risk tissues would have to submit information to the agency to receive premarket approval.

Thus, some products, such as dura mater, would be subject to lesser regulatory requirements than apply currently. The agency would be also able to reduce the regulatory burden for other products. For example, the agency would regulate heart valves as tissues, with no premarket approval requirements, rather than as devices with evaluation and approval requirements. For stem cells intended to reconstitute blood in a patient whose own ability to do so has been destroyed, the agency expects to be able to develop class-wide standards based on clinical data to be submitted by stem cell researchers. The new standards would obviate the need for detailed submissions in support of requests to investigate or market such products in patients not closely related to the cell donor.

In sum, the proposed approach would enhance both public health and public confidence in the safety and utility of cells and tissues, while imposing minimum burden on researchers and tissue facilities. Innovative new technologies that utilize cells and tissues for therapies would be regulated only to the extent appropriate to protect public health. The promulgation of consistent and rational rules also would enable product developers to anticipate regulatory requirements, and would thereby greatly facilitate their work.

THE REGULATORY FRAMEWORK IN DETAIL

As noted previously, cells or tissues that are removed from a patient and transplanted back into that same patient during a single surgical procedure would not be regulated. For all other cellular and tissue-based products encompassed in the plan, the regulatory obligations would be determined by an analysis of the five public health and regulatory areas, as described below.

Transmission of communicable disease. Cells and tissues can transmit infectious diseases, which makes infectious disease controls critical. The agency would require that certain donor screening and donor or tissue testing procedures be followed when the cells or tissue will be used in someone other than the donor him/herself, or, for reproductive tissue, in a person not sexually intimate with the donor. The screening and testing requirements would depend on the communicable disease risks presented by the different types of cells or tissue. However, in most cases, there would be no required submissions to the agency regarding the testing and screening.

For cells and tissues to be used in the person from whom they were obtained, or in sexually intimate partners of reproductive-tissue donors, the agency would only recommend that screening and testing procedures be followed. The agency would require that record keeping and labeling reflect the performance or omission of the recommended tests and the results, and that the use of material from infected or high-risk donors, or from untested or unscreened donors, be contingent on informed consent. However, the agency would not interfere with the choices made by the family and physician.

Handling and processing. The agency would subject all uses of cells and tissues other than in a single surgical procedure to either good tissue practices (GTPs) or good manufacturing practices (GMPs). Both GTPs and GMPs would encompass handling procedures aimed at preventing contamination and preserving cellular and tissue function and integrity; however GMPs would encompass additional processing controls as needed to ensure clinical safety and effectiveness.

GTPs would apply to products whose characteristics and uses do not raise clinical safety and effectiveness issues that call for marketing approval requirements. GMPs would apply to products that do raise such concerns and for which the agency would require marketing approval. To the extent that the GTPs and GMPs would cover the same areas of concern (i.e., handling and minimal processing), they would be the same.

For products subject to premarketing approval, the agency also generally would require premarketing submissions demonstrating that the products were manufactured according to validated controls and met product specifications.

Clinical safety and effectiveness. The agency would not require that all cellular and tissue-based products undergo clinical safety and effectiveness testing under regulatory controls. The agency would subject products to premarketing clinical safety and effectiveness study and approval requirements only if they are more-than-minimally manipulated such that their biological or functional characteristics may have been altered; are used for a function other than that which they normally perform or, for structural tissues, used in a location where such structural function is not normally performed; are combined with noncell or nontissue components; or are used for a metabolic function. (However, as mentioned previously, the agency would not impose these regulatory requirements on the use of minimally manipulated cells or tissue for their normal metabolic purpose in the donor or in a patient closely related to the donor.) Any of these factors raises issues of clinical safety and effectiveness in addition to the communicable disease concerns discussed above.

In cases where FDA had not stated whether a particular kind of processing was more-than-minimal manipulation or a particular use was not for normal function, the agency would expect innovators to make that determination themselves based on general information provided by FDA. However, FDA would encourage individuals to seek the agency's guidance when they have questions about the appropriate regulatory procedures. To respond to such inquiries, the agency is establishing a Tissue Reference Group consisting of three staff members from the agency's Center for Biologics and three staff members from the agency's Center for Devices. Sponsors would also have access to the agency's Office of the Ombudsman and Chief Mediator to address such matters.

The use of cells or tissue in a combination product with drugs, biologics, or mechanical or

synthetic devices raises clinical safety issues that are associated with those noncellular and nontissue products. Such combination products would continue to be regulated according to their primary mode of action (that is, depending on how they act, as a device, drug, or biologic).

Metabolic products raise potentially serious systemic safety and effectiveness issues. For example, the use of nonfunctional (and therefore ineffective) stem cells to reconstitute the cellular elements of the blood of a patient whose own stem cells have been destroyed by chemotherapy may lead to the death of that patient. Because of the higher level of concerns associated with metabolic products, they would receive close study and scrutiny.

However, while important medical issues exist for metabolic tissue used in the patient from whom it was obtained or in a close blood relative, as a policy matter the agency would not require premarketing approval for family use of such tissue when it is minimally manipulated, used for its normal function, and without noncell/nontissue components.

The agency intends to adjust its approval requirements, in particular for the clinical data on safety and effectiveness, in accordance with the types of tissues and cells, and their uses. Thus, the agency generally would review structural tissues requiring premarketing approval in accordance with standards for clinical safety and effectiveness data that apply to comparable devices, while it would review tissues used for metabolic functions in accordance with the standards that apply to licensed biologics.

Additionally, the agency would call on industry and academia to submit manufacturing and product standards designed to ensure safety and effectiveness of specific product-use classes for which supporting clinical data exists or may soon exist in the public domain. At present, the agency believes that such standards can be developed over the next two years for stem cells intended for hematopoietic reconstitution. The agency would phase in the licensure requirements as the standards were formulated. For products for which such standards were developed and adopted by the agency, applicants could certify that they met the standards and would not have to submit individual applications containing clinical data to receive licensure.

Promotion and labeling. The agency would require that promotional claims and labeling be clear, accurate, balanced, and nonmisleading. For products subject to premarket approval, the current labeling requirements applicable to biological drugs and devices would apply; in all other

cases, the sponsor would be obliged to label the products clearly and accurately, but no submissions to FDA would be required.

The agency would require labeling and/or record keeping as to what required or recommended testing and screening procedures were carried out, and the results of such procedures. The agency would allow labeling as to whether additional tests or procedures, such as retesting after quarantine, were carried out.

For products not subject to premarket approval, the agency would limit promotional claims to those for normal uses of the cells or tissue. Thus, the agency would allow stem cells for hematopoietic reconstitution, or for hematopoietic reconstitution in the case of chemotherapy-induced stem cell ablation or Fanconi's anemia. Claims for non-normal use (e.g., stem cells to treat melanoma) would trigger a requirement that the sponsor demonstrate safety and effectiveness for such claims and obtain premarket approval.

Baseline knowledge of industry (registration and listing). The agency has been criticized by government oversight bodies for not knowing "who is doing what" regarding cellular and tissue-based products. The agency is developing a simple electronic registration and listing system under which all establishments procuring, processing, shipping, banking, or distributing cellular or tissue-based products would be required to register with the agency and list their products. The agency would use this system for monitoring purposes and to distribute new information regarding guidances, policies, or requirements.

In sum, the agency has tried to develop a regulatory approach for cellular and tissue-based products that would treat like products alike, that would be flexible and allow innovators to develop new therapies with a minimum regulatory burden, and that would establish standards to protect the public health. The agency has sought to distinguish between the kinds of uses of human cells and tissues that required only minimal regulatory oversight, and the kinds of uses of human cells and tissues that warrant greater surveillance.

IMPLEMENTATION

Implementation of this initiative will be carried out through a phased approach:

- 1) Making available to the public a detailed document describing the proposed regulatory framework.
- 2) Holding a public meeting with industry and other interested parties to discuss and refine the approach.
- 3) Engaging in notice and comment rulemaking for new rules, such as for registration and listing, screening and testing requirements, GTPs, and labeling.

New requirements, as well as the application of existing requirements to new product classes, would be phased in over the next two to three years.

PROPOSED NEW REGULATORY FRAMEWORK FOR HUMAN TISSUE

CONCERN 1: DISEASE TRANSMISSION (Does the Tissue Pose a Risk of Transmitting Diseases Such as AIDS or Hepatitis?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
Tissue transplanted within one person that has been banked, processed, or shipped	Disease screening and testing recommended; Good Tissue Practices (GTPs) (handling, recordkeeping, and labeling procedures) would be required	None
Tissue donated from one person to another	Subject to GTPs; disease screening and testing would be required	None

CONCERN 2: CONTROL OF PROCESSING
(What Kinds of Handling and Processing Controls Would Be Necessary?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
Minimally processed structural ³ tissue used for its normal function and having no nontissue parts; or reproductive tissue ⁴ used for its normal function, and having no non-tissue parts	Would be subject to GTPs relating to contamination, integrity, and function	None
Minimally processed metabolic tissue ⁵ transplanted into the same person, or into a family member, used for its normal function, and having no nontissue parts	Would be subject to GTPs relating to contamination, integrity, and function	None
Metabolic tissue transplanted to another person not related to the donor; or that has been manipulated, or is used for other than its normal function, or has nontissue parts	Would have more comprehensive processing controls than GTPs (to address clinical safety/effectiveness concerns)	Human testing exemptions and marketing approval by FDA would be required. (In certain cases, certification to standards may substitute for data submission.)
Structural tissue that has been manipulated, or is used for other than its normal function, or has nontissue parts	Would have more comprehensive processing controls than GTPs (to address clinical safety and effectiveness concerns)	Human testing exemptions and marketing approval by FDA would be required.

³ Structural tissue comprises such tissue as corneas, ligaments, bones, cartilage, tendons, dura mater, and heart valves.

⁴ Reproductive tissue comprises such tissue as ova, semen, and embryos.

⁵ Metabolic tissue is tissue that affects the function of the entire body (e.g., umbilical cord stem cells infused into a patient to reconstitute the cellular elements of the patient's blood, or pancreatic islet cells implanted to treat diabetes).

CONCERN 3: CLINICAL SAFETY

(Does the Product Need FDA Approval for Safety/Effectiveness?)

Product Characteristic	Industry Action Required	Submission to FDA
Minimally processed structural tissue used for its normal function, and without nontissue parts; or metabolic tissue that is used in the same person or in a close relative of the donor that is minimally processed, used for its normal function, and has no nontissue parts.	None	None
Tissue used for structural reconstruction or repair that: 1) has been manipulated; or 2) is used for other than its normal function; or 3) is combined with nontissue parts	Would have to gather clinical safety and effectiveness data	Human testing exemptions and marketing approval required; standard for effectiveness determination would be consistent with that for comparable devices
Metabolic tissue used in a person not related to the donor, or that: 1) has been manipulated; or 2) is used for other than its normal function; or 3) is combined with nontissue parts	Would have to gather clinical safety and effectiveness data	Human testing exemptions and marketing approval by FDA required; standard for effectiveness determination would be consistent with that for biologics
Reproductive tissue that is: 1) manipulated; 2) used for other than its normal function; or 3) combined with nontissue parts	Would have to gather clinical safety and effectiveness data	Human testing exemptions and marketing approval by FDA required; standard for effectiveness determination would be consistent with that for biologics.

CONCERN 4: CLAIMS MADE BY MANUFACTURERS
(What Regulation Is Needed of Product Labeling and Advertising?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
All other tissue	Clear, accurate, balanced, and nonmisleading labeling and promotion	No FDA submission concerning labeling for products regulated only under section 361; for products regulated under section 351 and/or FDC Act, normal rules would apply

CONCERN 5: BASELINE KNOWLEDGE OF INDUSTRY
(Should Tissue Products Be Registered with FDA?)

Product Characteristic	Industry Action Required	Submission to FDA
Tissue transplanted within one person during a single surgical procedure	None	None
All other tissue	Notification of FDA	Registration and listing under new regulation under 361 or under section 510 of the FDC Act

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National Performance Review

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OVERVIEW

INTRODUCTION

One of the Food and Drug Administration's (FDA's) many responsibilities is assuring that drugs used to treat animals are safe and effective. The agency has worked hard to ensure the expeditious and predictable review of animal drugs and other related therapeutic products. However, the overall process of developing a new drug is complex, and a significant period exists between the first introduction of the drug into animals and formal submission to FDA, completion of review by FDA, and approval of the drug for marketing. The reforms in this proposal address both the process undertaken by the sponsor before the application is submitted to FDA, as well as the review by FDA after the agency has received the application.

Faster Approvals: The New Animal Drug Re invention Initiative

To speed up the drug approval process, FDA is implementing a set of policies that will enable faster approval of new animal drugs. The new animal drug reinvention initiative will introduce numerous new process changes and programs to create a more streamlined new animal drug application review and approval process. Although the reforms that comprise this initiative are relatively new, they have been positively received by sponsors. FDA proposes to re-write the new animal drug application (NADA) regulations to provide timeframe incentives for each step of the new process and thereby further encourage participation. The reform proposal is detailed below.

FDA'S PROPOSAL FOR REFORM

Re-engineering the New Animal Drug Approval Process

Background: Historically, FDA has reviewed new animal drug applications using a process that has emphasized centralized coordination of the application's review throughout a project. FDA has also required the submission of a single application package that included data and other information necessary to address all possible efficacy, human food safety, animal safety, and drug manufacturing questions. While this system had some advantages -- it ensured a single location for administrative processing and quality control -- it also resulted in delays in application processing. For example, because the project manager was solely responsible for communication with the sponsor, delays could occur in communicating to the sponsor the results of technical review of a portion of a new animal drug application (NADA). In addition, even though important scientific issues concerning safety or efficacy were often identified by FDA experts, such discoveries and new-data requests were too often spread out over an extended period, unnecessarily prolonging the total review time. Furthermore, FDA had no centralized means of tracking all applications under review in the Center, and therefore, no way of monitoring overall review performance and progress.

Proposal and Justification: Under this initiative, FDA has begun to introduce numerous new process changes and programs that will enable a more streamlined animal drug application review and approval process, and which would result in less regulatory burden upon industry.

Implementation of pre-submission conferences: In a change from past practice, FDA is now encouraging sponsors of new animal drug applications to participate in pre-submission conferences during which FDA and the sponsor discuss in detail what studies are necessary to demonstrate the safety and effectiveness of the drug for its intended indications and conditions of use. The purpose of holding pre-submission conferences is to get agreement between FDA and the sponsor on the studies necessary to obtain approval for the desired drug claims. To date, these conferences have decreased instances where sponsors conduct studies, but after review, FDA determines that the information is not pivotal in making the final decision on

approvability. This process will eliminate unnecessary studies, save drug companies significant resources, and contribute substantially to more expeditious marketing of new products.

Implementation of protocol reviews: FDA has begun to encourage sponsors to submit review protocols for the studies to be conducted in support of a NADA. Once FDA agrees to a protocol, it is committed to no "moving targets" unless significant, new scientific issues arise. These commitments enable FDA reviewers to evaluate studies in a more timely manner, and sponsors to embark on a development plan with a more certain understanding of FDA's requirements. FDA will propose regulations mandating a timeframe for the agency's completion of its protocol review.

New program of "phased review" of data submissions: During pre-submission conferences, sponsors are being encouraged by FDA to identify the critical studies and timeframes in their drug-development plans. FDA will commit to review these studies individually in the sequence most advantageous to the sponsor. For example, FDA will review a dose-determination study prior to the sponsor conducting trials for efficacy and target animal safety, thus allowing the sponsor to ensure that subsequent research is conducted with the formulations and doses that have been confirmed to be effective.

Direct review of sponsors' technical submissions: FDA has begun to implement a new approach to submission review in which review responsibilities are decentralized. Under this approach, each individual conducting a technical review on the submission is responsible for the scientific evaluation and administrative processing of a particular section of a submission, and communication with the sponsor on that particular technical review. Under the previous system, each animal drug application had a single project manager, who was responsible for parceling out work assignments to technical reviewers and communicating with the sponsor. The new decentralized system encourages more expeditious reviews and more direct communication between appropriate FDA reviewers and drug sponsors by eliminating the "middle man," which means that the appropriate FDA technical reviewers will now speak directly to the sponsor's technical experts. Although CVM (Center for Veterinary Medicine) senior review managers will maintain oversight of the process, with the assistance of STARS (see below), the resolution of technical questions on one part of the submission will no longer be likely to interfere with the review process for other parts of the submission.

Utilization of sponsor-monitored methods trials: In order for a new animal drug to be approved, there must be a practical analytical method available that is capable of detecting residues of the drug in tissue of food-producing animals. In the past, FDA and sponsor companies had been dependent on government laboratories for evaluation of analytical methods, which often have higher priorities than evaluation of animal drug analytical methods. FDA now allows sponsors to contract with private

laboratories to conduct methods trials. FDA evaluates the results of the trials and determines the acceptability of the method.

New requirements for data quality assurance: FDA has undertaken a program designed to improve the quality of the data contained in animal drug applications. This program has two parts: (1) a major effort to improve guidance to the animal drug industry regarding quality assurance for data collection, analysis, and reporting, and (2) an effort to have sponsors assume greater responsibility for data quality assurance. In order to implement this program, FDA plans to propose regulations requiring that sponsors certify that NADA data have been subjected to a quality assurance audit.

Implementation of the Submission Tracking and Reporting System (STARS): In November 1992, FDA started using a new computer system. This system enables FDA to set prioritized time frames for each submission based on the purpose of the submission and the amount and complexity of the submission's data. STARS is critical to FDA's ability to monitor the status of pending applications and other files. Furthermore, STARS enables FDA to much more efficiently coordinate scientific reviews among individual reviewers and reviewing divisions as the reviews move forward in an interactive process among reviewers and the sponsor. FDA will propose regulations committing to these prioritized timeframes.

Updated regulations and guidance documents: Largely due to declining resources, FDA had for some years been unable to review and update existing regulations and guidance documents or to prepare new ones. Recognizing the value of such documents, especially in the drug development process, FDA has renewed its commitments in this area. FDA will soon propose regulations for the investigational and new animal drug application processes, as well as guidance regarding responsibilities of clinical investigators, and manufacturing chemistry issues. Several more documents are in development, including guidance on efficacy studies for production drugs intended to change carcass quality/leanness, efficacy and target animal safety requirements for anticoccidial, anthelmintic, and mastitis drugs.

Impact: These new initiatives will streamline the NADA approval process. For example, pre-submission conferences are essentially eliminating what sponsors and others in the animal health industry have referred to as the "moving target," in which FDA specifies the studies necessary for approval in an iterative fashion over a protracted period. Phased review has removed a common bottleneck caused by the fact a sponsor had to wait until all technical sections were reviewed before FDA would render an opinion on the sufficiency of an application. As a result, the technical section in the application that required the longest review could stymie progress on other sections. Under phased review, however, sponsors can coordinate submission of each technical section as the work for that section is completed. In addition, the direct

review program, when linked with phased review, has resulted in significantly improved and more interactive communication between sponsor and reviewer, enabling a more efficient and logical review process.

These changes, while relatively new, have been positively received by sponsors. Because the reform initiative is presently being implemented, very few applications have been completely reviewed under the initiative's reformed procedures. However, it is clear from FDA's experience with those applications that have had the final stages of review take place under the reformed procedures that fewer iterations occur in which FDA must ask for additional data and the sponsor must go back to produce the data. Elimination of each iteration represents a time savings. Although only a few NADA approvals have been reviewed under these procedures, the average total time for their review was less than that for applications reviewed the traditional way. The most recent animal drug approval under this program was issued 22 days after filing -- all of the substantive review having already taken place while the drug was still in testing.

While drug sponsors are pleased with the added efficiency of the program, they have expressed concern over the lack of statutory timeframes for review. Therefore, FDA will propose new regulations for animal drug applications and testing that will provide FDA's commitment to prioritized review timeframes -- all of which will be shorter than the current statutory timeframe of 180 days.

Implementation and Timeline: All of these program changes are being implemented now by FDA. Proposed regulations describing the administrative process and FDA's commitment to application-review timeframes will publish in 1997. Guidelines for study protocol development, clinical investigator guidelines (which include data quality assurance guidelines), and manufacturing chemistry guidelines are expected in late 1997, after publication of the regulations. Guidelines for efficacy studies for production drugs intended to change carcass quality/leanness are expected before the end of 1997, and guidelines for efficacy and target animal safety requirements for anticoccidial, anthelmintic, and mastitis drugs will be produced in early 1998.

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JULY 1995