Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 312, and 601

[Docket No. 00N–0989]

Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics licensing regulations regarding confidentiality of information. The amendments would add provisions that would make available for public disclosure, and require submission for public disclosure of, certain data and information related to human gene therapy or xenotransplantation. The proposed regulation would apply specifically to the areas of human gene therapy and xenotransplantation because these areas of clinical research have the potential for unique public health risks and modification of the human genome. The proposed rule would provide for public disclosure of certain data and information related to an investigational new drug application (IND), to provide an opportunity for public education on, and discussion and consideration of, public health and safety issues. In addition, the proposed rule would require sponsors of clinical trials on human gene therapy or xenotransplantation to submit to FDA for public disclosure certain data and information that has been redacted to remove or obscure all information defined as confidential commercial or trade secret, or names and other personal identifiers of patients and certain other third parties.

DATES: Submit written comments on this proposed rule on or before April 18, 2001. Submit written comments on the information collection provisions by February 20, 2001.

ADDRESSES: Submit written comments on this proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to Wendy Taylor, FDA Desk Officer, Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Building, 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background Information

A. Current FDA Policies Regarding Disclosure of Information

FDA regulations in part 312 (21 CFR part 312) provide procedures that govern the use of investigational new drugs, including new biological drugs, in humans. Under part 312, the sponsor of a clinical study in humans must submit to FDA an IND which provides specific information regarding the investigational new drug and the clinical study. The IND must be authorized by FDA and approved by the local institutional review board (IRB) before the clinical study may begin. The provisions of this rulemaking do not alter the procedures specified in part 312 for submission of an IND. A manufacturer requesting approval to market a biological product in interstate commerce must submit a biologics license application (BLA) to FDA before the product may be introduced into interstate commerce (42 U.S.C. 262). Among other things, the BLA contains information and data resulting from the clinical studies performed under an IND (§ 601.2 (21 CFR 601.2(a))). All information and data concerning the product, including those submitted in applicable IND's and in the BLA, are held by FDA in a biological product file (see definition of ''biological product file'' in § 601.51(a) (21 CFR 601.51(a)) throughout the lifetime of the product.

The general requirements related to disclosure of information for all types of commodities regulated by FDA and for all types of documents are provided in part 20 (21 CFR part 20). Under these regulations, certain categories of information are exempt from mandatory disclosure. The categories of information relevant to human gene therapy and xenotransplantation clinical trials that have historically been exempt from public disclosure include trade secrets and commercial or financial information which is privileged or confidential (§ 20.61); personnel, medical, and similar files, the disclosure of which constitutes a clearly unwarranted invasion of personal privacy (§ 20.63); and at the discretion of FDA, interagency or intra-agency memoranda or letters, except for factual information which is reasonably segregable (§ 20.62).

Specific requirements for the availability for public disclosure of data and information in an IND, including those IND's relating to biological drug products, are included in § 312.130. FDA's policy for the confidentiality of data and information contained in an IND for a biological product and in a biological product file is provided in §§ 601.50 and 601.51 (21 CFR 601.50 and 601.51). Under §§ 601.50 and 601.51, and consistent with the other referenced disclosure regulations, FDA has not routinely publicly disclosed any data or information contained in an IND or a pending biological product file. FDA has not even acknowledged the existence of the IND or a pending biologics license application, unless its existence has previously been publicly acknowledged. Because the agency has no mechanism for reliably tracking what information concerning an unapproved, investigational product has been publicly acknowledged, the agency generally provides no information to the public concerning an investigational product, including information concerning any IND or pending BLA submissions, and refers the public to the sponsor of the IND or the pending biological license for further information. In some cases, FDA may publicly disclose selected portions of safety and effectiveness data, such as summary information for consideration at an open session of a Federal advisory

committee meeting, or other public workshops or meetings (§ 601.51(d)(1)). Once a biological license has been approved, certain information, as specified in § 601.51(e), concerning the approved product and the clinical investigation of the product may be publicly disclosed.

B. Issues Related to Human Gene Therapy and Xenotransplantation

As a result of rapid advances in molecular biology, genomics, immunology, and transplant biology, new classes of biological therapeutics are being developed with the goal of providing future treatment options for genetic disease, cancer, and organ failure. Novel therapeutic approaches currently under consideration include the areas of human gene therapy and xenotransplantation. Human gene therapy and xenotransplantation are being proposed to treat genetic diseases such as cystic fibrosis, cardiovascular insufficiency, metabolic diseases such as diabetes, neurologic diseases such as Parkinson's and Huntington's disease, cancer, acquired immune deficiency syndrome (AIDS), and organ failure.

1. Definitions

Human gene therapy is defined as the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use. Cells may be modified ex vivo for subsequent administration to the subject or altered in vivo by gene therapy products given directly to the subject. Human gene therapy includes, but is not limited to, autologous or allogeneic bone marrow stem cells modified with a viral vector, intramuscular or intravascular injection of a therapeutic plasmid deoxyribonucleic acid (DNA) or a therapeutic viral vector, ribozyme technology, and use of sequence specific oligonucleotides to correct a genetic mutation. For the purposes of this regulation, gene therapy is not intended to include the administration of viral or cellular products (e.g., blood or unmodified bone marrow), or their derivatives, that do not contain genetic material that has been specifically engineered into the product for therapeutic purposes. While prophylactic vaccines, including plasmid DNA vaccines and genetically modified viral vector vaccines, and some replication competent viruses are excluded under this regulation from the gene therapy definition, they are similar in nature to gene therapy products. Issues relevant to gene therapy products, such as vector integration and biodistribution, also apply to prophylactic vaccines. Therefore, the agency requests comment on whether such products should be included under this rulemaking to allow information related to these products to be available for public disclosure.

The use of antisense oligonucleotides to block gene transcription is not intended to be included under gene therapy; however, as noted above, the use of sequence specific oligonucleotides to correct a genetic mutation would be included. The proposed mechanism of action of sequence specific oligonucleotides is to irreversibly change, insert, or delete a single base in the genome of a cell. This raises questions of whether base changes may result in mutations that may cause cancer, or express an immunogenic protein or have other adverse health affects. In addition, their use in vivo raises issues of activity in tissues other than the target and the risk of gonadal biodistribution leading to germ line changes.

Xenotransplantation refers to any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (1) Live cells, tissues, or organs from a nonhuman animal source; or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs. The live cells, tissues, or organs used in xenotransplantation are referred to as xenotransplantation products. Xenotransplantation products include those from transgenic or nontransgenic animals, as well as combination products that contain xenotransplantation products in combination with drugs or devices. These include, but are not limited to, porcine fetal neuronal cells, encapsulated porcine islet cells, encapsulated bovine adrenal chromaffin cells, baboon bone marrow, and external liver assist devices employing porcine liver, or porcine hepatocytes. Nonliving biological products or materials from animals, such as porcine heart valves and porcine insulin, are not classified as xenotransplantation products for the purposes of this rulemaking.

2. Public Health Issues

While human gene therapy offers great promise for improving the lives of patients with serious, life-threatening diseases and disorders, there are several risks inherent in its use as a medical intervention. These risks include the inadvertent infection of patients, and potentially their contacts, with replication competent virus present in gene therapy vector preparations. For example, infection with type C murine retroviruses, which could contaminate retroviral vector preparations, is known to cause a range of diseases in animals including spongiform encephalopathy, anemia, and neoplastic disease. In addition, these risks include the risk of infection with novel infectious agents generated by recombination in vivo, the consequences of which are unknown; the risk of insertional mutagenesis through disruption of the normal genetic sequence, resulting in altered gene expression; and the risk of inadvertent modification of the patient's germline and its effect on future offspring.

Although xenotransplantation provides a potential approach to address the shortage of human organs and for treatment of disease, the use of xenotransplantation products raises concerns about possible infection of the recipient and, subsequently, the public at large with both known and as-yet-unrecognized infectious agents. Experience with human allograft transplantation has demonstrated the potential for transmissibility of infections from donor to recipient through transplants (Refs. 1 to 3). The direct contact resulting from implantation of a xenotransplantation product into a recipient, with the associated disruption of anatomical barriers and the immunosuppression of the recipient, may facilitate interspecies transmission of xenogeneic infectious agents. The potential for subsequent transmission of a xenogeneic infectious agent from the recipient to the recipient's close contacts, and propagation through the general human population, is an additional risk and a recognized public health concern.

Insertional mutagenesis is a risk potentially associated with the infection of xenotransplant recipients and their close contacts and the general population with xenogeneic retroviruses. In addition to potential horizontal transmission of infectious agents from the recipient of a xenotransplantation product to the recipient's contacts, there is concern regarding vertical transmission of infectious agents from the recipient to progeny during gestation (e.g., transmission from mother to fetus of infectious agents across the placenta or during parturition). Vertical transmission of xenogeneic infectious agents could result in the development of infectious disease in progeny. In addition, vertical transmission of xenogeneic viruses can result in insertional mutagenesis with disruption of normal human development or integration into the germline resulting in transmission to future generations.

Thus, human gene therapy and xenotransplantation investigative approaches individually pose: (1) Risks that extend beyond the individual (e.g., public health risks, including the potential for the transmission of infectious agents from the recipient to the public at large); and (2) risks of inadvertent modification of the germline (alterations of the genetic material of the progeny). Moreover, these approaches may also be used in combination (e.g., xenotransplantation products genetically modified before implantation), resulting in complex questions and issues for consideration and discussion prior to and during human clinical trials.

3. Public Education and Informed Consent Issues

Human gene therapy and xenotransplantation investigations call for additional mechanisms to provide the public access to clinical trial information relevant to the assessment of risks and benefits, and to informed consent. Special care is needed to ensure that individual subjects understand the experimental nature of the procedures and their known and unknown risks and burdens. Human gene therapy and xenotransplantation require the evaluation of risks to third parties such as health care workers, close contacts of the recipient, and the community. The informed consent process should address the need for long-term surveillance and post-mortem analysis and potential infectious disease risks to recipients and their contacts.

These investigative approaches raise new challenges for the local review bodies responsible for ensuring the safe and ethical conduct of this research. Local IRB's are responsible for reviewing biomedical and behavioral research involving human subjects, to protect the rights of human subjects (45 CFR part 46, Protection of Human Subjects, and 21 CFR part 56, Institutional Review Boards). Institutional Biosafety Committees (IBC's) are responsible for reviewing and overseeing basic and clinical research conducted at their institutions. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment (section IV–B–2 National Institutes of Health (NIH) Guideline for Research Involving Recombinant DNA Molecules). This proposed rule would provide a mechanism for public access to human gene therapy and xenotransplantation clinical trial information and for public education, informed discussion and participation that can form a foundation for safe and ethical research in these innovative areas.

The proposed rule would enhance the development of related Federal initiatives that provide for public access to clinical trial information through national data bases: There are also a number of Internet sites sponsored by associations, clinical centers or academic institutions, and nonprofit organizations that provide public access to similar types of clinical trial information. Examples include: Center Watch Clinical Trials Listing Service at http://www.centerwatch.com, a resource both for patients interested in participating in clinical trials and for research professionals; http://www.HealthAtoZ.com, a search engine for health and medical Internet resources; the Musella Foundation for brain tumor research and information, at http://www.virtualtrials.com; the National Alliance of Breast Cancer Organizations, at http://www.nabco.org, which, in an effort to increase awareness of clinical trials, lists brief descriptive summaries of clinical trials in the National Cancer Institute Physician Data Query (NCI PDQ) data base; the University of Michigan, at http://www.cancer.med.umich.edu, which lists clinical trials at the University of Michigan Cancer Center (UMCC) and supplies links to external clinical trials and resources; the former Surgeon General C. Everett Koop's Internet site, at http://www.drkoop.com, which allows the public to browse through a listing of therapeutic areas where volunteers are being sought for clinical trials; Biotechnology Industry Organization, a trade association, at http://www.bio.org, which lists press releases and industry news, and provides links to patient groups and professional medical societies; and http://www.investor.biospace.com, which has not only a biotechnology search engine that links to hundreds of companies, but also extensive information on the latest technologies and clinical trials, as a basis for investment. The proposed rule should facilitate the development of similar data bases, either publicly or privately sponsored, with information concerning the study of gene therapy and xenotransplantation. As provided under section 113 of the Food and Drug Modernization Act of 1997 (Public Law 105–115), NIH, through its National Library of Medicine, has created a national clinical trials data base at http://clinicaltrials.gov to provide patients, family members, and other members of the public with current information about clinical research studies.

4. Basis for Disclosure

Historically, public disclosure of information with regard to human gene therapy and xenotransplantation has assisted FDA in performing its duties and has benefitted the public. The categories of information that may be made publicly available by FDA as a result of this disclosure rule include information currently made public by other Federal agencies in connection with advisory committee meetings or other public workshops or meetings, and through general commercial disclosure.

The NIH Office of Biotechnology Activities (OBA; formerly the Office of Recombinant DNA Activities) administers the Recombinant DNA Advisory Committee (RAC). This committee was established in October 1975, in response to concerns about the potential public health risks and environmental hazards posed by recombinant DNA research, as well as the significant ethical, legal, and societal issues associated with this emerging technology. The RAC has met quarterly in open public session to discuss these issues and, since the first human gene transfer clinical trial was proposed in 1988, the committee has publicly reviewed selected human gene transfer clinical trial protocols. The minutes of RAC discussions of human gene transfer clinical trials and related issues are accessible to the public via the OBA website (http://www.nih.gov/od/oba/index.htm). RAC review and public discussions provide an important mechanism for receiving public input into Federal policy development and for making the public aware of potential toxicities and adverse events associated with gene transfer products. As one example, when a participant in a cystic fibrosis gene transfer clinical trial required intensive care treatment for an acute adverse event suffered shortly after administration of an adenoviral gene transfer product, the investigator was invited to discuss the occurrence with other experts in the field at the next public RAC meeting. This public discussion and analysis facilitated both dissemination of important information about this toxicity and enhanced understanding of its pathogenesis, thereby contributing to the safety of patients in other gene therapy trials.

NIH also collects information on gene transfer studies and makes it available to the public. Appendix M of the ''NIH Guidelines for Research Involving Recombinant DNA Molecules'' (Ref. 4) requires that investigators provide specific information for the purposes of protocol registration, RAC review, and

potential public discussion, and that this information should not contain confidential commercial information or trade secrets, enabling all aspects of RAC review to be open to the public. The required information includes scientific and nontechnical abstracts, the informed consent document, statements on privacy and confidentiality, reports of serious adverse events, protocol amendments, and annual followup reports. Public disclosure of this information has facilitated progress and has contributed to improved patient safety in the field of human gene transfer by providing public access to clinical trial information, rapid dissemination of adverse event information, and summary information regarding outcomes of gene therapy clinical trials and adverse events.

All investigators receiving any NIH funds for basic and/or clinical research involving recombinant DNA molecules, and all investigators affiliated with institutions receiving any NIH funds for basic and/or clinical research involving recombinant DNA molecules, must comply with the NIH Guidelines. The NIH Guidelines also apply to collaborations between NIH-funded or affiliated researchers and privately funded investigators. In addition, commercial sponsors not affiliated with a NIH-funded institution have voluntarily submitted materials to OBA for RAC review. Therefore, the general practice in the field of human gene transfer has been to submit to NIH, OBA the information required under NIH Guidelines with the understanding that the information will be available for RAC review and potentially public discussion. This suggests that the information specified in Appendix M is not generally considered to be proprietary and that its disclosure does not impede commercial development.

The categories of information that would be disclosed as a result of this rulemaking include information that generally has been made public for xenotransplantation protocols. Sponsors of xenotransplantation IND's have publicly disclosed information regarding the scope of xenotransplantation clinical trials and the development of public health safeguards through: (1) Open public sessions of the Xenotransplantation Subcommittee of the Biologics Response Modifiers Advisory Committee (BRMAC) for the Center for Biologics Evaluation and Research (CBER), FDA (December 17, 1997, June 3 and 4, 1999, and January 13, 2000), and (2) Public Health Service (PHS) sponsored public workshops, including the workshop entitled ''Developing U.S. Public Health Policy in Xenotransplantation,'' January 21 and 22, 1998, at which xenotransplantation clinical trials under FDA IND's were summarized by the sponsor or by a sponsor's designee. Transcripts of these meetings can be found on the CBER Internet site at http://www.fda.gov/cber. At these public meetings, FDA scientists and others presented data demonstrating that porcine endogenous retroviruses could be activated and could infect human cells in vitro, and the implications of these data for porcine xenotransplantation product development and regulation were discussed. Based on these discussions, the BRMAC concurred with FDA's decision to place all porcine xenotransplantation clinical trials on clinical hold. During these meetings, FDA publicly discussed testing requirements and results needed by manufacturers in order to address and remove the clinical hold, and allowed sponsors of porcine xenotransplantation IND's the opportunity to present testing strategies, assuring the industry of consistency in regulation. The public as well was assured that Federal oversight was being conducted in a responsible manner.

Information related to the categories of information FDA proposes to disclose is available through publicly accessible filings to the Securities and Exchange Commission (SEC). The Securities Act of 1933 requires that investors receive financial and other significant information concerning securities being offered for public sale. In an annual filing, a company must provide a comprehensive overview of its business. This includes a description of ongoing research programs including discussion of clinical study safety and efficacy results, disclosure of investigational sites and the investigators involved, plans for product development and commercialization, and financial information. This information may be found on the SEC Internet site at http://www.sec.gov/edgarhp.htm.

In addition, voluntary disclosure of information regarding clinical trials of unapproved products and therapies by individual sponsors over the Internet has become widespread. Company Internet sites often provide this information in the form of descriptive summaries of clinical trials, press releases, recruitment opportunities for patients, investment opportunities, and general awareness material.

Thus, information of the kind FDA proposes to disclose concerning clinical trials on human gene therapy and xenotransplantation is already widely disclosed. This disclosure has not impeded commercial development of these products. In addition, the agency considers public disclosure of data and for information from human gene therapy or xenotransplantation clinical trials essential for public education, and for informed discussion and consideration of the public health and safety risks associated with the use of these investigational therapies.

II. Overview of Proposed Rule

A. Scope

The scope of this proposed rule is limited to disclosure of information related to human gene therapy and xenotransplantation. Confidential commercial information, such as information regarding commercial licensing agreements or the identification of suppliers, trade secret manufacturing information, names and other personal identifiers of patients and, except as specifically provided in the regulations, names and personal identifiers of third parties, such as physicians, hospitals, etc., and, at FDA's discretion, interagency or intra-agency memoranda and letters would not be disclosed. FDA is proposing only to disclose certain information necessary to ensure a continued mechanism for public education and input, which FDA believes is essential to the evaluation of the public health impact of these new technologies. FDA believes that these categories of information have not been considered to be proprietary, since they have been made publicly available through various mechanisms and their disclosure has not impeded commercial development. The public expects the current level of information disclosure and public review to continue in the areas of human gene therapy and xenotransplantation where there is potential risk to the public health.

The categories of information related to an IND that would be disclosed under this regulation include: (1) Product and patient safety data and related information, including results from preclinical and clinical studies and tests that demonstrate the safety and/or feasibility of the proposed procedures; (2) the name and address of the sponsor; (3) the clinical indications to be studied; (4) the protocol for each planned study, to include a scientific abstract and a nontechnical abstract, a statement of the objectives, purpose, and rationale of the study, the name and address of each investigator, the name and address of the official contacts of each local review body as appropriate (IRB, IBC) and dated copies of approval by each group, the criteria for patient selection and

exclusion, an estimate of the number of patients to be studied, a description of the treatment that will be administered to patients, and the clinical procedures, laboratory tests, or other measures to be taken to monitor the safety and effects of the drug in human subjects and to minimize risk; (5) written informed consent forms; (6) identification of the biological product(s) and a general description of the method of production, including a description of product features that may affect patient safety; (7) IND safety reports; (8) information submitted to FDA in the annual report; (9) the regulatory status of the investigation, the date of such action, and the reason for such action; and (10) other relevant data and information that the Director, CBER, determines are necessary for the appropriate consideration of the public health and scientific issues, including relevant ethical issues, raised by human gene therapy or xenotransplantation.

To facilitate public disclosure of this information, FDA proposes to require sponsors of human gene therapy and xenotransplantation clinical trials to submit to FDA the information defined above upon submission of: (1) The initial IND, (2) any amendment documenting changes or additions to the IND, at the time the amendment goes into effect, (3) IND safety reports, and (4) annual reports. FDA is not proposing to require the submission of any new information not previously submitted as part of the IND process. For example, FDA is not proposing that all variations and updates of informed consent forms be submitted to FDA for public disclosure; however, under the proposed rule, FDA would disclose any sample informed consent forms generally submitted with an initial IND submission.

The agency requests comment on whether this rulemaking should apply to information as defined above that is submitted in a BLA. Public disclosure of information in a BLA would provide a continuation of the availability of information for public disclosure up until the time of license approval. A disadvantage would be the amount of documentation that would be required to be submitted in order to support this initiative.

The proposed provisions of this rulemaking do not alter the procedures specified in part 312 for submission of an IND. However, with regard to clinical holds of an IND (§ 312.42), FDA would be able to place a human gene therapy or xenotransplantation investigation on clinical hold if the sponsor does not submit to the agency the redacted version of data and information for public disclosure, or if the redacted version submitted is incomplete or not properly redacted.

B. Legal Authority

The proposed regulation would make available for public disclosure specified safety and effectiveness information submitted in support of an IND [1] involving either a human gene therapy or xenotransplantation protocol. This information, discussed thoroughly in section II.C of this preamble, includes protocols, criteria for patient selection and exclusion, summary results of preclinical and clinical studies of the investigational article, a summary of the treatment that will be administered and the measures that will be taken to minimize risk to human subjects, safety reports, informed consent documentation, and information concerning the regulatory status of the product, such as whether it is on clinical hold and the reason for the hold. While such information relating to human gene therapy protocols has routinely been made available to the public through the NIH RAC process for the last 20 years, FDA regulations have consistently provided that similar information submitted to FDA as part of an IND is not publicly available. (See §§ 601.50 and 601.51.) This proposed rule is an attempt to harmonize these approaches for public review of important, new, but potentially hazardous and controversial, therapies. In this way, FDA will be able to more fully participate in existing and future venues for obtaining educated public input and discussion that could inform the agency's deliberations. The agency believes that there is great benefit in having human gene therapy and xenotransplantation products scrutinized, as they are being developed, by individuals with a wide variety of perspectives, including scientists from different disciplines, biomedical ethicists, patient advocacy organizations, and the general public, because of the unique blend of proposed benefit as well as potential risk to society that these products possess. Investigations of these types of products raise serious ethical and scientific issues, and, therefore, the decisionmaking process should be as transparent and fully informed as possible.

The proposed rule would formalize the existing practice of making certain specified types of safety and effectiveness information in IND's for human gene therapy and xenotransplantation publicly available. Such disclosure is necessary in order to protect the public health by informing the research community and the public of the nature and the hazards of the proposed research and by permitting comment on the merits of the proposed research.

The Freedom of Information Act (FOIA), 5 U.S.C. 552, generally provides that Federal agencies must disclose information in their files to the public on request. FOIA is designed to make federal agency records or information available to the public. The Supreme Court has stated that, ''The basic purpose of [the] FOIA is to ensure an informed citizenry, vital to the functioning of a democratic society, needed to check against corruption and to hold the governors accountable to the governed.'' (See *NLRB* v. *Robbins Tire & Rubber* Co., 437 U.S. 214, 242 (1978).)

The statute provides nine exemptions and three law enforcement exclusions that agencies may use to protect specific categories of information from disclosure (5 U.S.C. 552(b)). These exemptions are the only basis for withholding information requested by the public under the FOIA [2] and are discretionary, not mandatory. (See *Chrysler Corp.* v. *Brown*, 441 U.S. 281 (1979).) One of these exemptions is particularly relevant to this proposed rule and the disclosure of information in applications to investigate and market human gene therapy and xenotransplantation products.

Exemption 4 of the FOIA protects trade secrets and confidential commercial information from public disclosure. (See 5 U.S.C. 552(b)(4).) While trade secret information, narrowly defined as secret, commercially valuable information related to manufacturing methods or processes, is present in all IND's and biological product files, including those subject to this proposed rule, this

[1] While human gene therapy and xenotransplantation protocols are generally regulated by CBER as biological products, it is possible that some of these products may be combination products consisting of biological components, drug components, and device components. The same rules of disclosure will apply to the drug or device components of combination products under the same theories discussed later in this section.

[2] It should be noted here that section 301(j) of the act prohibits the public disclosure of information, obtained under certain sections of the act, ''concerning any method or process which as a trade secret is entitled to protection.'' (See 21 U.S.C. 331(j).) In addition, the so-called Federal Trade Secrets Act also contains certain restrictions on the public disclosure of trade secret and confidential commercial information. The Trade Secrets Act does provide for the disclosure of confidential commercial information where such disclosure is ''authorized by law.'' (See 18 U.S.C. 1905.)

proposal will not affect the confidentiality of such information, and therefore it will not be discussed. Confidential commercial information is defined under exemption 4 as ''commercial or financial information obtained from a person and privileged or confidential.'' Each element of the definition must be satisfied for information to be confidential commercial information entitled to protection under exemption 4.

Historically, much of the data and information submitted in IND's and unapproved biological product files has been considered confidential commercial information. (See *Public Citizen Health Research Group* v. *FDA*, 704 F.2d 1280 (D.C. Cir. 1983); *R & D Laboratories, Inc.* v. *FDA* No. 00–CV–0165 (D.D.C. Sept. 7, 2000).) FDA's general information disclosure regulations define confidential commercial information, and provide that information submitted to FDA that falls within this definition is not disclosable. (See 21 CFR 20.61.) Further, the regulations that apply to the submission of IND's and biological product files define the contents of these applications as confidential commercial information generally exempt from disclosure and, indeed, even prohibit the agency from acknowledging the existence of an application (prior to approval) if it has not already been publicly disclosed. (See 21 CFR 312.130, 601.50, and 601.51.) The regulations provide different rules for disclosure after an approval letter has been sent, and when the application has been terminated, abandoned, or otherwise no longer has commercial value.

The agency is exercising its legal authority to promulgate new regulations that will make explicit and will formalize the circumstances and means by which certain safety and effectiveness information in these special types of applications will be made available for public disclosure. Such a change is especially warranted when, as here, the change is being made in large part to reflect the actual environment in which human gene therapy and xenotransplantation applications exist.

As has been discussed elsewhere in this preamble (in section I.B, Issues Related to Human Gene Therapy and Xenotransplantation), sponsors of IND's pertaining to human gene therapy have publicly disclosed the types of information covered by this proposed rule for many years as part of the process overseen by the RAC. Likewise, there has been widespread practice in the field of xenotransplantation to make publicly available a great deal of information concerning details of trials of xenotransplantation products during public advisory committee meetings and workshops sponsored by FDA and by the U.S. PHS. Information that is publicly disclosed by its owner cannot be confidential within the meaning of the FOIA and, as a result, can be made available for public disclosure by FDA. (See *CNA Fin.* v. *Donovan*, 830 F.2d 1132, 1154 (D.C. Cir. 1987).) The fact that these types of information cannot be considered confidential is the principal basis for issuing this proposed rule.

This proposed rule contains the public disclosure procedures the agency will apply to the safety and effectiveness information in human gene therapy and xenotransplantation applications that has historically been treated as confidential commercial information by the agency. These procedures will follow the consistent practice in the fields of human gene therapy and xenotransplantation of making such information available to the public. It is important to note that while certain safety and effectiveness data and information will be publicly available under this proposed rule, FDA does not intend to disclose the full reports of safety and effectiveness on the basis of which the product may be approved. FDA believes that, prior to approval of a biological product file, the full reports constitute confidential commercial information, as they traditionally have under the agency's regulations, and should not be released. (See 21 CFR 601.51(d).) However, under § 601.51(e), all safety and effectiveness data and information do become publicly available after a license is issued, and this practice will not be changed by this proposal.

In addition to the full reports, the agency also wishes to make clear that it will continue its current policy of not releasing confidential commercial information that is contained in a human gene therapy or xenotransplantation IND or unapproved biological product file. Examples of confidential commercial information that may exist in these applications would include information concerning licensing agreements and information identifying suppliers. This information ordinarily will remain confidential under exemption 4 unless it has already been publicly disclosed by the sponsor. Such business-related information is also not the type of information that FDA believes should be disclosed to further the public discussion and evaluation of human gene therapy and xenotransplantation trials. In addition, this proposed rule will not affect the rules governing the disclosure of personal medical and other similar information, the disclosure of which would cause an unwarranted invasion of personal privacy. (See 21 CFR 20.63.)

Based on the authorities discussed, the agency proposes to require sponsors of IND's related to human gene therapy and xenotransplantation to disclose certain specified safety and effectiveness data and information. This proposal will formalize and codify the existing practice in these fields under which these data and information have been publicly disclosed by their sponsors. Disclosure is especially necessary regarding these new, important, and also controversial technologies so that the research community and the public can be assured of the safety of conducting clinical trials of these products.

This proposal would require the sponsors of human gene therapy or xenotransplantation IND's to submit to FDA publicly available versions of information FDA requires in such IND's. The purpose of this requirement is to facilitate FDA's efforts to make important information concerning human gene therapy and xenotransplantation IND's available to the public in a timely and efficient manner. Sponsors would have to redact the information from IND submissions specified in proposed § 601.53. Sponsors would redact trade secrets, confidential commercial information, such as licensing agreements and suppliers, and names and other personal identifiers of patients and, except as specifically provided in the regulations, names and personal identifiers of third parties, such as physicians, hospitals, etc. (See §§ 20.61 and 20.63.) It would not be necessary for sponsors to redact the vast majority of the information in human gene therapy and xenotransplantation IND's since, as described in this proposal, such information would be publicly disclosable.

The proposed rule would also specify that FDA may place a human gene therapy or xenotransplantation investigation on clinical hold if the sponsor has not submitted to the agency a redacted and thus disclosable version of the required IND information that complies with the requirements of proposed § 601.53. A sponsor must properly purge its redacted version of trade secrets, confidential commercial information, and names and other personal identifiers and, except as specifically provided in the regulations, names and personal identifiers of third parties, such as physicians, hospitals,

etc. Section 505(i)(3) of the act authorizes FDA to prohibit a sponsor of an investigation from conducting that investigation if FDA determines that the drug involved represents an unreasonable risk to the safety of persons who are the subjects of the clinical investigation, or if there are other reasons that FDA has established by regulation for which the agency may issue a clinical hold. FDA recognizes that errors in redacting may occur and will provide sponsors with an opportunity to correct such errors. However, FDA will have the enforcement authority to place a human gene therapy and xenotransplantation investigation on clinical hold if resolution is not reached on any discrepancies found by FDA in the redacted versions, or if a redacted version is not submitted at all by the sponsor. As described in this proposal, it is important for proposed and ongoing human gene therapy and xenotransplantation investigations to be the subject of public education, discussion, and consideration in order for all relevant issues, including safety, to be explored.

As stated above, FDA has tentatively concluded that the information that would be disclosed as a result of this rulemaking is, in fact, already being made public through a variety of mechanisms, and therefore cannot be considered confidential. As such, it does not constitute confidential commercial (or trade secret) information within the meaning of FOIA Exemption 4.

However, FDA's issuance of this proposed rule is authorized even if the information to be disclosed could be considered confidential commercial information covered by Exemption 4 and within the scope of protection of the Trade Secrets Act (18 U.S.C. 1905). That statute prohibits the disclosure of confidential commercial or trade secret information, except as ''authorized by law.'' Because agency regulations that specifically provide for the disclosure of such information can supply the requisite legal authorization for release of the information for purposes of the Trade Secrets Act, that statute would not present a bar to any of the disclosures contemplated by this proposed rule. (See, e.g., CNA Financial Corp., 830 F.2d 1132, 1138–1139 (D.C. Cir. 1987)).

The broad rulemaking authority conferred on FDA by Congress under the act (21 U.S.C. 201 *et seq.*) permits the agency to amend its regulations as contemplated by this proposed rule.

Section 505(i) of the act (21 U.S.C. 355(i)) gives FDA the authority to issue regulations imposing conditions on the investigation of new drugs. In addition to prescribing certain mandatory conditions, that section further provides that the agency may impose ''other conditions'' as necessary ''relating to the protection of the public health.'' (21 U.S.C. 355(i)). This language was added to the act as part of the Drug Amendments of 1962 (Public Law 87–781) to make it ''clear that the conditions prescribed in the [bill] are not the sole conditions that may be imposed for the protection of public health.'' H.R. Conf Rep. No. 2526, at 20 (1962), reprinted in 1962 U.S.C.C.A.N. 2927, 2929. Legislative history relating to these amendments also indicates that one purpose of the bill was to make ''information on drugs * * * more readily available to physicians and the general public.'' (S. Rep. No. 1744, at 1 (1962), 1962 U.S.C.C.A.N. 2884). FDA's broad discretion in adopting regulations under this language has been upheld by the courts. (*United States* v. *Garfinkel*, 29 F.3d 451 (8th Cir. 1994)).

The proposed amendments to FDA's regulations are within FDA's statutory discretion in imposing conditions on products under development to promote the public health. The public health often is served not only by collection of research data and information, but also by disclosure of such information. (See e.g., *Dole* v. *United Steelworkers of America*, 494 U.S. 26, 28 (1990)).

The proposed rule would serve several significant public health goals. It would enhance the ability of patients with serious and life-threatening diseases and others seeking information about emerging therapies to obtain critically important information from FDA about the existence of clinical trials in which they might participate, about possible safety problems associated with the products they are taking, and about the regulatory status of applications pending before the agency.

As an aftermath of recent problems in clinical trials involving gene therapy products, FDA and NIH have launched two new initiatives to further strengthen the safeguards for individuals enrolled in clinical studies for gene therapy. One initiative, the Gene Therapy Clinical Trial Plan, would ensure: That sponsors meet their obligation to adequately monitor the clinical trials for which they are responsible; that there is appropriately independent oversight of such clinical trials; and that there is an increased level of government oversight, through increased inspection frequency and review of sponsors' monitoring plans and other clinical trial practices. Under the other initiative, FDA and NIH will, several times per year, convene Gene Transfer Safety Symposia to provide a critical forum with experts in gene transfer for the sharing and analysis of medical and scientific data from gene transfer research. FDA and NIH support will also be provided for professional organizations and academic centers to hold safety conferences focused on gene therapy. These safety symposia and educational outreach efforts are intended to guide the conduct of current clinical trials and enhance the design of future gene transfer trials to maximize public safety.

The ready availability of information concerning clinical trials involving gene therapy is essential to the success of these efforts. For example, such information would be discussed at the government's safety symposia, may be made available for other scientific discussions and to the general public, and would be used in evaluating current gene therapy practices, including sponsor monitoring and informed consent standards. Likewise, FDA intends to continue to sponsor and support government, professional, and academic conferences related to xenotransplantation. Thus, FDA believes that the disclosure of information contained in INDs related to gene therapy and xenotransplantation trials is essential to patient safety and appropriate informed consent.

In addition to section 505(i), section 701(a) of the act (21 U.S.C. 371(a)) gives FDA general rulemaking authority to issue regulations for the efficient enforcement of the act. A regulation issued under section 701 of the act will be sustained as long as it is reasonably related to the purposes of the act. (*United States* v. *Nova Scotia Food Prod. Corp.*, 568 F.2d 240, 246 (2d Cir. 1977)). Section 903(b) of the act (21 U.S.C. 393(b)) explicitly states that the mission of FDA includes the promotion and protection of the public health. It has long been recognized by the courts, including the Supreme Court, that the primary purpose of the act is the protection of public health (*United States* v. *An Article of Drug, Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). As a result, FDA's rulemaking authority under section 701(a) of the act has been broadly construed to uphold a wide variety of the agency's rulemaking activities intended to protect the public health. (See e.g., *National Ass'n of Pharmaceutical Mfrs.* v. *FDA*, 637 F.2d 877 (2d Cir. 1981)) (current good manufacturing practice regulations); *Pharmaceutical Mfrs. Ass'n* v. *FDA*, 484 F. Supp. 1179 (D. Del. 1980) (rule requiring disclosure of drug side effects to patients); *American Frozen Food Inst.*

v. *Mathews*, 413 F. Supp. 548 (D.D.C. 1976) (rule establishing common and usual names for certain nonstandard foods to provide consumers with relevant buying information), *aff'd*, 555 F.2d 1059 (D.C. Cir. 1977); *National Nutritional Foods Ass'n* v. *Weinberger*, 376 F. Supp. 142 (S.D.N.Y.) (rule requiring that certain vitamin preparations be restricted to prescription sale and be labeled accordingly), *aff'd*, 512 F.2d 688 (2d Cir. 1975)), *cert. denied*, 423 U.S. 827 (1975). FDA believes that its rulemaking authority under section 701(a) of the act supports the amendments proposed here because they advance public health goals concerning gene therapy and xenotransplantation studies.

FDA is also proposing to issue this new regulation under the authority of section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264). Under section 361 of the PHS Act, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. (See sec. 1, Reorg. Plan No. 3 of 1966 at 42 U.S.C. 202 for delegation of section 361 of the PHS Act authority from the Surgeon General to the Secretary, Health and Human Services; see 21 CFR 5.10(a)(4) for delegation from the Secretary to FDA.) Intrastate transactions may also be regulated under section 361 of the PHS Act.

This proposed regulation is part of a regulatory program that will further the goal of preventing the introduction, transmission, or spread of communicable disease. For this regulatory system to be effective in preventing the spread of disease, FDA must be able to regularly make publicly available information regarding these experimental procedures. By providing sponsors, clinical investigators, patients and their families, and the general public with access to the types of information proposed in this rule, FDA will be able to more rapidly identify and react appropriately to newly discovered or understood risks in order to prevent the spread of communicable disease.

Studies in the areas of gene therapy and xenotransplantation are conducted to explore the potential for considerable benefits. However, use of these procedures, particularly in the case of xenotransplantation, poses potential risks for the transmission of infectious disease. Infectious disease public health concerns focus not only on the transmission of known zoonoses, but also on the transmission of infectious agents as yet unrecognized. The disruption of natural anatomical barriers and immunosuppression of the recipient increase the likelihood of interspecies transmission of xenogeneic infectious agents. An infectious agent may pose risks if it can infect, cause disease in, and transmit among humans, or if its ability to infect, cause disease in, or transmit among humans remains inadequately defined. The public availability of information this proposed rule envisions will permit public attention to any emerging risks associated with these experimental techniques, early detection and definition of which will permit the agency and sponsors to take steps to prevent or minimize the introduction of communicable disease.

An additional concern is that these infectious agents could subsequently be transmitted from the patient to family members and other close contacts of the patients, to health care personnel, and to other members of the public. Because the potential risk of transmission of infectious disease extends beyond the patient receiving the treatment, it is vital that the public, as well as the patient, be informed and educated about potential infectious disease risks and methods for reducing those risks. Close contacts should understand the uncertainty regarding the risks of xenogeneic infections, behaviors known to transmit infectious agents from human to human (e.g., unprotected sex, breast feeding, intravenous drug use with shared needles, and other activities that involve potential exchange of blood or other body fluids) and methods to minimize the risk of transmission. Close contacts of recipients also need to know about the importance of reporting any significant unexplained illness through their health care provider to the research coordinator at the institutions where the xenotransplantation was performed. This broader concern for the spread of communicable disease is reflected in the proposed requirements providing for public disclosure. While informed consent procedures may try to address these educational needs, the public release and discussion of information that this proposed rule calls for is also necessary to ensure that all those potentially at risk have the information to manage these risks and so avoid or minimize the spread of communicable disease.

For all the above reasons, to promote and protect the public health, FDA is proposing to issue this proposed rule providing for public disclosure of certain information relating to gene therapy and xenotransplantation.

C. Discussion of the Proposed Rule

The proposed rule would create a new § 601.52 entitled ''Availability for public disclosure of certain data and information related to human gene therapy or xenotransplantation'' and § 601.53 entitled ''Submission to FDA of certain data and information related to human gene therapy or xenotransplantation for public disclosure.'' In addition, conforming amendments are proposed to §§ 20.100, 312.42, 312.130, 601.50, and 601.51. The provisions of this rulemaking do not alter the procedures specified in part 312 for submission of an IND. The proposed regulations are discussed below.

1. Sections 601.50 and 601.51

Part 601 (21 CFR part 601) sets forth provisions that govern the licensing of biologic products by the FDA. Existing procedures and requirements regarding confidentiality of data and information contained in IND's for biological products or biologics license applications are described in §§ 601.50 and 601.51. The proposed rule would amend §§ 601.50 and 601.51 to include language that would reference the exceptions proposed in § 601.52 regarding the availability for public disclosure of certain data and information related to human gene therapy or xenotransplantation. Specifically, §§ 601.50(a) and 601.51(a) would be amended to add the words, ''Except as provided in § 601.52.''

In addition, FDA is proposing to amend the § 601.50 section heading and § 601.50(a) to replace the word ''notice'' with ''application'' to be consistent with other current regulations regarding investigational new drugs, i.e., part 312.

2. Proposed § 601.52

Proposed § 601.52 would set forth the requirements regarding the availability for public disclosure of certain data and information related to human gene therapy or xenotransplantation. These provisions would define the therapies and scope of the proposed regulation, and describe the types of data and information related to human gene therapy and xenotransplantation that may be disclosed by FDA.

a. *Definitions.* Proposed § 601.52(a) would include definitions of human gene therapy and xenotransplantation that are consistent with existing agency policy and guidance regarding these therapies. Proposed § 601.52(a)(1) would define ''human gene therapy'' to mean the administration of genetic material in order to modify or manipulate the expression of a gene

product or to alter the biological properties of living cells for therapeutic use. FDA interprets this definition to include both the ex vivo and in vivo modification of cells. Proposed § 601.52(a)(2) would define ''xenotransplantation'' to mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (a) Live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs. This definition of xenotransplantation does not include the use of products that are nonliving, acellular products such as porcine heart valves, porcine insulin, or bovine serum albumin. The definition also does not include non-animal cells and tissues, such as bacteria and plant cells.

Because the terms ''human gene therapy'' and ''xenotransplantation'' are not currently used elsewhere in the regulations, FDA is proposing that, for the convenience of the user, the definitions be included in proposed § 601.52. If, in the future, additional regulations are issued using these terms, FDA intends to move these definitions to the section of the regulations which currently includes definitions of other terms applicable to biological products (21 CFR 600.3).

b. *Scope*. Proposed § 601.52(b) would describe the scope of the proposed regulation. Consistent with the use of the terms ''human gene therapy'' and ''xenotransplantation,'' FDA intends that the proposed rule apply to the procedures, not specific products used in the therapies, although data and information regarding a product may be disclosed as proposed in § 601.52(c). FDA intends with this broadly-defined scope that the proposed regulation apply to any experimental use of human gene therapy and xenotransplantation, although the immediate impact of the proposed regulation would be on investigational products. For example, the proposed regulations would apply to any use of gene therapy or xenotransplantation in clinical studies in humans, including use of a licensed gene therapy or xenotransplantation product with an experimental drug or device being clinically studied for use in a gene therapy or xenotransplantation procedure.

FDA believes it is not necessary to disclose for purposes of public education and discussion all the information which may be included in an IND. Except as specifically provided in the proposed rule, FDA intends that information regarding human gene therapy or xenotransplantation investigations will continue to be held confidential, consistent with existing regulations in §§ 20.61, 20.62, 20.63, 20.100, 312.130, 601.50, and 601.51. Accordingly, proposed § 601.52(b) would specify that, except as specifically provided in proposed § 601.52, the availability for public disclosure of data and information related to human gene therapy or xenotransplantation shall remain in accordance with § 601.50 for IND's for a biological product.

c. *Information for public disclosure.* Proposed § 601.52(c) would specify the types of data and information related to human gene therapy or xenotransplantation that the FDA may make available for public disclosure. The types of information listed in proposed § 601.52(c) are already required for submission under existing regulations (parts 312 and 601) as part of an IND or BLA or as a supplement to a BLA.

Under proposed § 601.52(c)(1), FDA would make product and patient safety data and related information related to human gene therapy and xenotransplantation available for public disclosure. This proposed provision is similar to existing requirements in § 601.51(e)(1), which require that all safety and effectiveness data and information contained in a biological product file be made available for public disclosure immediately after a license has been issued. The proposed provisions in § 601.52, however, would extend this throughout the entire product development process for a product related to human gene therapy or xenotransplantation. The proposed rule further specifies in § 601.52(c)(1) that for the purposes of this proposed regulation, product and patient safety data and related information include results of preclinical and clinical studies and tests that demonstrate the safety and/or feasibility of the proposed procedures. In addition, FDA proposes in § 601.52(c)(1) to identify some of the types of product and patient safety data and related information that would be disclosed to the public that are particularly relevant or specific to human gene therapy and xenotransplantation. These types of product and patient safety data and related information are: (1) Analysis in animals, humans, or in vitro systems of gene transfer, expression, and persistence; (2) vector biodistribution; (3) evidence for immune response/anergy; (4) biological activity; (5) results of product safety testing including test results for known xenogeneic and human infectious agents and replication competent virus; (6) qualification of source herd, individual source animal, and source organ/tissue/cells for xenotransplantation in humans; and (7) information on monitoring or prevention of potential health risks to the recipient, close contacts, and health care workers. FDA does not intend this to be an exclusive list. In all cases, names and other personal identifiers of patients and, expect as specifically provided in the regulations, names and other personal identifiers of third parties, such as physicians or hospitals, would be removed. Furthermore, FDA does not intend product and patient safety data and related information under proposed § 601.52(c)(1) to include IND safety reports and annual reports, as provided for in §§ 312.32 and 312.33. Rather, specific requirements for the public disclosure of these types of reports are proposed below in § 601.52(c)(7) and (c)(8), respectively.

Under proposed § 601.52(c)(2) and (c)(3), FDA would make the name and address of the sponsor and the clinical indications to be studied available for public disclosure. The sponsor name and address and the indications to be studied are types of information that are consistent with information already required for submission to FDA in an IND under § 312.23(a)(1)(i) and (a)(3)(iv)(*b*), respectively.

Under proposed § 601.52(c)(4), FDA would make the protocol for each planned study available for public disclosure. A study protocol is required for submission in an IND under § 312.23(a)(6); proposed § 601.52(c)(4) would specify that certain elements of the protocol be available for public disclosure. Proposed § 601.52(c)(4)(i) through (c)(4)(vi) would describe the following specific elements of the protocol to be available for public disclosure: (1) A scientific abstract and a non-technical abstract; (2) a statement of the objectives, purpose, and rationale of the study (submitted in an IND under § 312.23(a)(6)(iii)(*a*)); (3) the name and address of each investigator (submitted in an IND under § 312.23(a)(6)(iii)(*b*)); (4) the name and address of the official contacts of each local review body as appropriate (IRB (submitted in an IND under § 312.23(a)(6)(iii)(*b*)), and IBC (NIH *Guidelines for Research Involving Recombinant DNA Molecules*, revised April 1998)) and dated copies of each committee's approval of the study; (5) the criteria for patient selection and exclusion and an estimate of the number of patients to be studied (submitted in an IND under § 312.23(a)(6)(iii)(*c*)); and (6) a description of the treatment that will be administered to patients and the clinical procedures, laboratory tests, or

other measures to be taken to monitor the safety and effects of the drug in human subjects and to minimize risk (similar to that submitted in an IND under § 312.23(a)(6)(iii)(*g*)). FDA intends that the term ''investigator' in proposed § 601.52(c)(4)(iii) include ''sponsor-investigators'' (individuals who have the responsibility for both the development and clinical investigation of the product) as well as ''investigators,'' both of which are defined in existing § 312.3(b). In proposed § 601.52(c)(4)(iv), FDA intends to make available for public disclosure the dated copies of the IRB's and IRC's approval of the proposed clinical study to identify when the IRB or IBC assumed responsibility for the continued review and approval of the IND.

Under proposed § 601.52(c)(5), FDA would make sample informed consent forms available for public disclosure. FDA proposes to provide public access to human gene therapy and xenotransplantation clinical trial information relevant to informed consent to promote public education, discussion, and consideration of the unique challenges that these novel therapies present to assuring adequate informed consent, as discussed previously in this proposed rule.

Under proposed § 601.52(c)(6), FDA would make the identification of the biological product(s) and a general description of the method of production, including a description of product features that may affect patient safety, available for public disclosure. This proposed provision contains types of information that are required for submission to FDA in an IND under § 312.23. FDA has modified the language taken from § 312.23 to reflect information needs related to human gene therapy and xenotransplantation and specifies that only a ''general'' description of the production method would be made available, excluding trade secret information. FDA does, however, propose to further specify in § 601.52(c)(6) that the identification and description would include the following types of information, as applicable: (1) The vector name and type; (2) gene insert; (3) regulatory elements and their source; (4) intended target cells; (5) source of cells, tissues, or organ(s); (6) method used to prepare the vector containing cells; (7) method used to procure and prepare cells, tissues, or organ(s) for xenotransplantation; (8) purity of cells; (9) adventitious agent testing; (10) description of the delivery system; (11) ancillary products used during production; (12) herd colony and individual source animal health maintenance and surveillance records; and (13) biological specimens to be archived from source animals. These types of information are consistent with information that is already submitted to and publicly disclosed by OBA for human gene therapy.

Under proposed § 601.52(c)(7), FDA would make IND safety reports, as provided in § 312.32, and other similar data and information available for public disclosure. Under § 312.32, sponsors of investigational drugs, including biological drugs, are required to submit to FDA certain adverse reaction reports concerning their product. Under § 601.51(e)(3), information concerning these adverse experience reports, excluding names and other identifiers of patients, health care facilities, and physicians, may be publicly disclosed after the licensure of the product. Under proposed § 601.52(c)(7), such adverse experience reports and other safety reports related to an investigational product could be publicly disclosed at any time throughout the lifetime of the product. The same limitations for disclosure included in § 601.51(e)(3) are included in proposed § 601.52(c) to protect the privacy of patients and health care workers.

Under § 601.52(c)(8), FDA would make information submitted in the annual report available for public disclosure. Sponsors must submit to FDA annual reports of the progress of the investigations as required under § 312.33. FDA proposes that the following types of information relevant to human gene therapy and xenotransplantation be included, as applicable, in the annual report submitted by the sponsor to FDA for public disclosure: (1) Evidence of gene transfer, gene expression in target cells, and biological activity; (2) assessment of immune response; (3) analysis of biodistribution; (4) significant preclinical and clinical toxicities; (5) evidence of infection by agents associated with the products; (6) adverse experiences; (7) number of subjects who died during participation in the investigation, with the cause of death for each subject and the status of autopsy requests; and (8) any available post mortem evidence of gene transfer, biodistribution, specifically including gonadal distribution. In all cases, names and other personal identifiers of patients and, except as specifically provided in the regulations, names and other personal identifiers of third parties, such as physicians or hospitals, would be removed.

Under proposed § 601.52(c)(9), FDA would make the regulatory status of the investigation, the date of a regulatory action, and the reason for an action available for public disclosure in order to identify to the public the current regulatory status of a clinical investigation. For example, FDA would disclose that an investigation is on clinical hold, or that an IND is inactive, withdrawn, or terminated. Additional information regarding the procedures and criteria for placing an investigation on clinical hold, withdrawal of an IND, inactive status for an IND, and IND termination may be found in §§ 312.42, 312.38, 312.45, and 312.44, respectively.

Under § 601.52(c)(10), FDA would make available for public disclosure other relevant data and information that the Director, CBER, determines are necessary for the appropriate consideration of the public health and scientific issues, including relevant ethical issues raised by human gene therapy or xenotransplantation. This proposed provision is included because the investigational nature of these therapies and the continuing evolution of the science surrounding these therapies renders FDA unable to anticipate all of the types of information related to human gene therapy and xenotransplantation that may warrant public education, discussion, and consideration. Examples of other relevant data that FDA may disclose could, under certain circumstances, include the details of a test used to determine eligibility for trial entry or autopsy or biopsy information. However, in general, FDA intends to release only the information specifically identified in this proposed rule, except in unique conditions or circumstances. Proposed § 601.52(c)(10) would provide that other relevant data and information may be approved for disclosure only by the Director of CBER.

3. Proposed § 601.53

Proposed § 601.53 would require sponsors of human gene therapy and xenotransplantation clinical trials to submit to FDA for public disclosure a redacted version of certain data and information. These provisions would specify when and what types of submissions to make to FDA in a redacted version for public disclosure, and the requirements for identifying and certifying these submissions.

Furthermore, proposed § 312.42(b)(6) provides that a sponsor's failure to submit to FDA the data and information specified in §§ 601.52 and 601.53 that has been properly redacted under § 601.53(a) is a basis for FDA placing the investigation on clinical hold. FDA recognizes that errors in redacting may occur and will provide sponsors with an

opportunity to correct such errors. However, FDA will have the enforcement authority to place a human gene therapy and xenotransplantation investigation on clinical hold if resolution is not reached on any discrepancies found by FDA in the redacted versions, or if a redacted version is not submitted at all by the sponsor. It is important that FDA has the specific authority to place a human gene therapy or xenotransplantation investigation on clinical hold if the sponsor has not submitted required data and information to FDA in a form that FDA can make publicly available in a timely and efficient manner. As previously described in this proposal, due to the unique nature of human gene therapy and xenotransplantation, public participation in the consideration of proposed and ongoing clinical studies of such therapies is crucial. In order for such public education, discussion, and consideration to take place and be meaningful, FDA must be able to make all relevant and publicly disclosable data and information available to the public as soon as practicable. The agency has determined that having sponsors submit redacted versions that comply with proposed §§ 601.52 and 601.53 is the most efficient means to accomplish this.

Under proposed § 601.53(a), FDA would require the sponsor of an IND to submit to FDA for public disclosure a redacted version of the types of submissions identified in § 601.53(b)(1) through (b)(5). The sponsor would be required to include all applicable information identified as disclosable in § 601.52 and redact all information considered confidential as trade secret, names and other personal identifiers of patients and, except as specifically provided in the regulations, names and personal identifiers of third parties, such as physicians, hospitals, etc., and certain confidential commercial information, such as information regarding commercial licensing agreements or the identification of suppliers. Sponsors would be permitted to redact either by removing or obscuring the information exempt from disclosure.

Proposed § 601.53(b)(1) through (b)(5) would list the types of submissions that the sponsor would be required to submit to FDA in duplicate and as a redacted version for public disclosure. FDA believes this information should be available for public disclosure as soon as possible and therefore, would require under this paragraph that the redacted version be submitted to FDA concurrently with the original unabridged submission or at the specific time points noted.

Proposed § 601.53(b)(1) would require submission for public disclosure a redacted version of the information defined under § 601.52 to accompany the original unabridged IND submission.

Proposed § 601.53(b)(2) would require submission for public disclosure a redacted version of any amendment documenting changes or additions to the information defined under § 601.52 that occur either during the IND review process or after the IND goes into effect. FDA recognizes that some amendments may require negotiation with FDA and subsequent revision by the sponsor. As such, FDA would require that the redacted version of any amendment be submitted at the time the amendment goes into effect.

Proposed § 601.53(b)(3) would require submission for public disclosure of a redacted version of any IND safety report at the time of submission of the original report to FDA. Sponsors are required under § 312.32 to notify FDA in a written IND safety report of any serious and unexpected adverse experiences associated with the use of their drug no later than 15 days after the sponsor's initial receipt of the information. FDA believes that the timely availability of adverse experience information is essential for public education and informed discussion and consideration of the health and safety issues presented by the experiences.

Proposed § 601.53(b)(4) would require submission for public disclosure of a redacted version of the annual report, in accordance with § 312.33. Consistent with § 312.33, sponsors would be required to submit, within 60 days of the anniversary date that the IND went into effect, a redacted version of the annual report.

Under proposed § 601.53(b)(5), a sponsor would be required to submit for public disclosure a redacted version of other information upon specific request of the Director, CBER. For example, FDA may request that the sponsor submit information regarding a test used to determine eligibility for trial entry. This proposed provision is included because due to the investigational nature of these therapies and the continuing evolution of the science surrounding these therapies, FDA is not able to anticipate all of the types of information related to human gene therapy and xenotransplantation that may warrant public education, discussion, and consideration. However, in general, FDA does not intend to request information not identified in this proposed rule, except for unique conditions or circumstances.

Proposed § 601.53(c) would require that the sponsor submit the information identified in § 601.53(b) in duplicate, in a form readily separable from the nonredacted or original unabridged version or submission and clearly marked as suitable for public disclosure on each page of the submission. This proposed provision would enable FDA to identify and provide this information more rapidly to the public and would help assure that only appropriate information is disclosed to the public.

Proposed § 601.53(d) would require that any copyrighted material be included in a single appendix to the submission and listed in a bibliography in the redacted version. The proposal would specify that any copyrighted material whose copyright is not owned by the applicant shall not be included in any other section of the redacted version. FDA is including this provision to facilitate timely release of the redacted version on the Internet. In response to an FOIA request, copyrighted materials can be included in the response. However, with regard to posting on the Internet, copyrighted material must be redacted prior to electronic disclosure as this is not considered a ''fair use'' of copyrighted material. Therefore, FDA would not release the appendix containing copyrighted materials as part of the redacted version on the Internet, but may release the bibliography of materials included in the appendix.

Proposed § 601.53(e) would require that redacted versions be accompanied by the statement specified to ensure that the sponsor has redacted only the information identified in § 601.53(a) as exempt from disclosure (confidential commercial, trade secret, or personal information). In addition, under proposed § 601.53, the sponsor must include a declaration that the statement is true and correct, under penalty of perjury.

4. Conforming Amendments

The proposed rule would make conforming amendments to parts 20 and 312. Part 20 describes the procedures and policy regarding the availability and disclosure of information to the public. Section 20.100 lists the cross-references to other sections of title 21 CFR that contain requirements on the availability of specific categories of FDA records and how these records are handled upon a request for public disclosure. The proposed rule would amend § 20.100(c) by adding a paragraph (43) that would contain a cross-reference to the proposed § 601.52 regarding the availability for public disclosure of certain data and information submitted

to FDA related to human gene therapy or xenotransplantation.

Part 312 describes the procedures and requirements that govern the use of investigational new drugs, including provisions for submission to and review by FDA of IND's. The provisions of this rulemaking do not alter the procedures specified in part 312 for submission of an IND. Section 312.42, among other things, lists the grounds for which FDA may impose a clinical hold of an investigation. Proposed § 312.42(b)(7) would amend § 312.42 by adding an additional basis for clinical hold for human gene therapy and xenotransplantation investigations. Under this proposal, FDA could place a human gene therapy or xenotransplantation investigation on clinical hold if the sponsor has not submitted to the agency a redacted version for public disclosure that complies with the requirements of § 601.53.

Section § 312.130 contains requirements regarding the availability for public disclosure of data and information in an IND. The proposed rule would amend § 312.130 by revising paragraph (b) to include a reference to proposed § 601.52, in addition to the existing references to §§ 601.50 and 601.51, when listing the provisions of this chapter that govern the availability for public disclosure of all data and information in an IND.

III. Implementation

Under the proposed rule, FDA would require that sponsors of human gene therapy and xenotransplantation clinical trials submit for public disclosure a redacted version of the information defined under § 601.52 as contained in the initial IND submission, amendments documenting changes or additions to the information defined under § 601.52 at the time the amendments go into effect, IND safety reports, and annual reports. The redacted version of these documents should be submitted to FDA in a form immediately releasable to the public, and clearly marked accordingly on each page of the submission as suitable for public disclosure. Acceptable approaches range from submitting a ''marked up'' version of the original that obscures the information which is not to be disclosed, to developing a separate document that abstracts the needed information for public disclosure from the original unabridged version submitted to FDA.

Specifically, FDA is proposing that the redacted version of the information specified in the proposed rule be submitted to FDA concurrently with the original unabridged IND submission or at the specific time points noted in the provisions. Sponsors of human gene therapy and xenotransplantation clinical trials would send an original and two copies of the original unabridged version of the IND submission (as required under existing § 312.23(d)) as well as one copy of the redacted version for public disclosure to FDA's CBER, where they would be received by the Document Control Center (DCC) to be logged, filed, and routed for appropriate documentation, review, and approval. DCC would route the submittals to the appropriate FDA reviewer, where, upon receipt, the redacted version for public disclosure would be reviewed for administrative completeness as well as to ensure that the submitting sponsor has appropriately redacted personal information regarding patients and third parties prior to release to the public. Once this review is complete, the redacted version for public disclosure would be sent to the Dockets Management Branch for public display where a docket number would be assigned. Each redacted version for public disclosure submitted to FDA would be tagged with the same docket number for that IND for reference. FDA is also proposing to make the redacted versions for public disclosure available to the public electronically on the Internet site according to the docket number.

In addition, to facilitate timely release by FDA of the redacted version, FDA is proposing to require that all copyrighted materials submitted in accordance with § 601.53 be placed in a single appendix and listed in a bibliography in the redacted version. Should an FOIA request be received for the data and information specified in § 601.52, FDA would be able to include a copy of any copyrighted materials in its response. However, FDA would not be able to publicly release any copyrighted material on the Internet as electronic posting of such information is not a ''fair use'' of that copyrighted material and must be redacted prior to electronic release. In this case, FDA instead would disclose the bibliography of copyrighted materials contained in the appendix.

FDA encourages, but would not require at this time, sponsors to submit the redacted version for public disclosure in electronic format. Pilot programs are currently underway regarding submission of electronic IND's and BLA's. (See 63 FR 29740 and 29741.) As such, FDA may, in the near future, implement electronic submission and disclosure of this information.

Sponsors of human gene therapy or xenotransplantation clinical trials who submit an initial IND or an amendment to an existing IND on or after the effective date of the final rule resulting from this rulemaking would be required to submit a redacted version for public disclosure in conformance with the rule.

Sponsors of xenotransplantation clinical trials who have submitted an IND to FDA prior to the effective date of the final rule resulting from this rulemaking would be required to submit for public disclosure a redacted version of the information defined under § 601.52, reflecting all amendments to date, by a date specified in the final rule.

Sponsors of human gene therapy clinical trials who have submitted IND's or amendments prior to the effective date of the final rule, need not submit redacted versions. For these IND's or amendments, FDA will rely on the existing OBA database as a source of the information that FDA will disclose.

For additional information regarding the proposed effective dates for the final rule see the end of this preamble.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts and Initial Regulatory Flexibility Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and under the Unfunded Mandates Reform Act (UMRA) (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. The UMRA requires that agencies prepare a written statement under section 202(a) of UMRA of

anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) in any one year.

The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. OMB has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. Aggregate impacts of the rule, and aggregate expenditures caused by the rule, will not approach $100 million for either the public or the private sector. As discussed below, because of the limited information that can be used to characterize the entities that may qualify as small businesses, the impact on small business establishments is uncertain. FDA has therefore prepared an Initial Regulatory Flexibility Analysis.

A. Background

In the discussion that follows, FDA will describe the purpose and requirements of the proposed rule, the estimated number of entities that will be affected, the estimated cost of compliance with the rule per IND, and a summary of estimated annual costs to industry.

The purpose of the proposed rule is to make available for public disclosure and to require submission in redacted version for public disclosure, certain data and information related to human gene therapy and xenotransplantation investigations. These areas of clinical investigation have the potential for unique public health risks and modification of the human genome. The public health and safety risks require that FDA be able to make timely disclosures of adverse outcomes, such as the development of novel infectious agents, unanticipated alterations of a recipient's germline, and severe toxicity resulting from the therapy, in order to prevent or contain further adverse occurrences.

These therapeutic research areas will effectively transform participating recipients into life-long research subjects. The length of commitment, coupled with the magnitude of potential risks to the recipients, their families and community, will present new challenges for risk assessment and the adequacy of informed consent. As noted earlier, these investigative approaches raise new challenges for Institutional Review Boards. The novelty and extent of the risk issues will call for expanded public access to clinical trial information relevant to assessment of risks and benefits, and public education and informed consent. These public information needs can only be addressed through disclosure of relevant information about the proposed and ongoing investigations.

The information to come under this disclosure regulation includes: (1) Product and patient safety data and related information including results of preclinical and clinical studies and tests that demonstrate the safety and/or feasibility of the proposed procedures; (2) the name and address of the sponsor; (3) the clinical indications to be studied; (4) the protocol for each planned study to include a scientific abstract and a nontechnical abstract, a statement of the objectives, purpose, and rationale of the study, the name and address of each investigator and subinvestigator, the name and address of the official contacts of each local review body as appropriate (IRB, IBC) and the dated copies of approval by each group, the criteria for patient selection and exclusion, an estimate of the number of patients to be studied, and a description of the treatment that will be administered to patients, and the clinical procedures, laboratory tests, or other measures to be taken to monitor the safety and effects of the drug in human subjects and to minimize risk; (5) the informed consent documentation; (6) the identification of the biological product(s) and a general description of the method of production, including a description of product features that may affect patient safety; (7) the IND safety reports; (8) the information submitted to FDA in the annual report; (9) the regulatory status of the investigation, the date of an action, and the reason for an action; (10) and other relevant data and information that the Director, CBER, determines are necessary for the appropriate consideration of the public health and scientific issues, including relevant ethical issues, raised by human gene therapy or xenotransplantation. After a license has been issued, all safety and effectiveness data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown (§ 601.51(e)(1)).

The sponsor of an IND involving human gene therapy or xenotransplantation will be required to submit this information in redacted version for public disclosure, removing all information that would be defined as trade secret, or personal information. The redacted submissions would be as follows:

1. Redacted version of information as defined under § 601.52 at the time of the initial IND submission.

2. Redacted version of any amendment documenting changes or additions to the information defined under § 601.52, at the time the amendment goes into effect.

3. Redacted version of IND safety reports at the time of submission of the initial report.

4. Redacted version of the annual progress report within 60 days of the anniversary date that the IND went into effect.

The redacted version would be submitted in a form that is readily identifiable and separable from the original unabridged submission to FDA.

The proposed rule will affect sponsors of human gene therapy or xenotransplantation clinical trials. The agency estimates that, at any one time, a total of 147 sponsors will be affected by the proposed rule. This includes 134 sponsors that have submitted IND's in the area of human gene therapy, and an additional 13 sponsors that have submitted IND's for clinical trials involving xenotransplantation. The number of new IND's per year in these two research areas has remained relatively constant at the level of approximately 45 IND submissions per year, for the past several years.

B. Cost Impact

Certain types of information have a substantial commercial value. This value may be particularly high for data pertaining to specific business plans, strategies, or lines of scientific research. The required disclosure of such information, however, imposes no economic impact where the relevant data are already available to competitors. As discussed earlier in this preamble, information that would be disclosed under this proposed rule is routinely examined and discussed by the RAC, in the case of gene therapy, and discussed at other public meetings addressing xenotransplantation issues, or through public filings with the SEC. Because the information proposed for disclosure has not been treated as confidential by industry, FDA finds that there is minimal incremental commercial value associated with the information that may be disclosed. The agency has, therefore, not attributed regulatory costs to its disclosure. The

agency requests public comment on the validity of this view.

The proposed rule will require additional paperwork activities for affected firms. The primary impact on clinical trial sponsors will be the requirement for additional staff time to redact IND-related submissions, throughout the period in which the IND is active. Table 1 of this document provides a summary of the types of submissions that will be required for public disclosure and the estimated number of such submissions that FDA expects to receive each year across all active IND's in the areas of human gene therapy and xenotransplantation. The estimated time required per redacted submission is also shown in table 1. The numbers of submissions and redaction times are estimated by FDA staff involved in application review, based on their experience in recent years, and their familiarity with the content of the IND packages. The redaction is assumed to be performed by a relatively senior member of the scientific research staff at a sponsoring organization. The cost per hour of staff time is estimated to be approximately $38, based on the Bureau of Labor Statistics estimate of total hourly compensation for professional white-collar workers in the private goods-producing and service producing industries.[3] The redacted documents listed in table 1 reflect a series of submissions that would typically occur over several years. Based on FDA's estimate of the total volume of submissions of each type per year, the agency estimates that the total cost to the industry will be approximately $123,880 [$41,040+$5,130+$1,710+$76,000]. This yields an average annual cost of $843 per sponsor [$123,880/147].

TABLE 1.—ESTIMATES OF COST PER YEAR FOR INDUSTRY-WIDE REDACTION EFFORTS

Type of Redacted Submission	Total Industry Submissions per Year	Average Redaction Time/Submission	Estimated Industry Cost per Year
New IND[1]—initial and authorized version	45	24 hours	$41,040 [45 x 24 x $38]
IND amendments	270	0.5 hour	$5,130 [270 x 0.5 x $38]
IND safety reports	90	0.5 hour	$1,170 [90 x 0.5 x $38]
Annual reports	100	20 hours	$76,000 [100 x 20 x $38]
Total Annual Cost to Industry			$123,880
Average Annual Cost Per Sponsor (147 sponsors)			$843

[1] Investigational new drug application.

C. Benefits

Although human gene therapy offers the promise of more effective treatment, for diseases ranging from cystic fibrosis to human immunodeficiency virus (HIV), rapid progress and patient safety in research requires timely communication of new findings about the success or risks of candidate strategies. The key to success for any human gene therapy strategy is attaining a vector that can serve as a safe and efficient gene delivery vehicle (Ref. 5). In general, human gene therapy researchers work to maximize efficacy through the regulation of gene expression over long periods (Ref. 6). Simultaneous with this goal, researchers attempt to develop vectors and treatment strategies that will both minimize the patient's immune response (which counters the therapy) (Ref. 7) and minimize the toxicity of the gene therapy (Refs. 8 and 9). As different vectors are considered, it is critical that newly discovered risks be reported to alert other researchers considering similar vectors or developing therapies to treat similar conditions.

As described earlier, the importance of timely communication of risks is clearly demonstrated by the cystic fibrosis patient who developed an acute adverse event requiring intensive care after receiving an adenoviral vector. In this case, public discussion of the adverse event at the RAC meeting facilitated rapid dissemination of important information about this toxicity, thereby contributing to the safety of patients in other gene therapy trials.

For xenotransplantation, the disclosure of information is necessary for public education and more efficient product and recipient tracking. Communication of risks offers other benefits for recipients of xenotransplantation products, their families, and their communities. According to a recent World Health Organization report on xenotransplantation, ''The practice of xenotransplantation carries with it an unquantifiable risk of xenozoonotic infection and disease. Measures are required to minimize risk and maximize safety in the potential use of this technology'' (Ref. 10). The level of risk is particularly difficult to quantify since potential viruses may be unknown and ''silent'' in the donor species; that is, they may not be identified through the currently available battery of screening tests for known pathogens. In addition, the risk of infection in the recipient of a xenotransplantation product may be substantially increased as a result of the immunosuppressive drug therapy administered to prevent rejection of the transplanted xenotransplantation product.

New evidence supporting the possibility of this risk is reported in a recent study (Ref. 11) showing that pig pancreatic islets transplanted into severely immunodeficient mice produce porcine endogenous retroviruses (PERV) that can infect human cells that had been transplanted into the same mice receiving the porcine pancreatic cells. Although pigs are considered a promising alternative source of organs for xenotransplantation, this study found that the PERV were trancriptionally active and infectious cross-species in vivo after xenotransplantation of the pig tissues. These findings bolster earlier concerns about PERV infection from pig islet

[3] U.S. Dept of Labor, Bureau of Labor Statistics, Employer Costs for Employee Compensation, March 1997.

xenotransplantation in immunosuppressed human patients.

Recent experience with zoonotic viruses has demonstrated the potential lethality of these viruses. An example is the 1998 to 1999 outbreak of a hendra-like virus in Malaysia and Singapore (Ref. 12). Documented cases occurred primarily among adults who had come in close contact with swine, which also showed signs of the illness. In some instances, illness in the pigs had occurred 1 to 2 weeks before illness in the humans. Illness in humans was characterized by 3 to 14 days of fever and headache followed by drowsiness and disorientation that often progressed to coma within 24 to 48 hours. During the period September 1998 to April 1999, 229 human cases were reported, 111 of which (48 percent) resulted in death. Although the first cases of human illness were reported in September 1998, the type and source of infection was initially unknown, so human exposures continued to occur, with the peak number of new cases occurring 6 months later, in March 1999. Once the type of virus was identified, through laboratory testing, and the source of infection (i.e., exposure to pigs) was serologically confirmed, public health measures were taken to prevent further outbreaks.

Ebola hemorrhagic fever is another disease that is transferable from animals to humans (Ref. 13) and consequently illustrates the importance of timely tracking of and public communication about zoonotic viruses. In the period from January to July 1995, a total of 316 persons became ill with hemorrhagic fever in Kikwit, Democratic Republic of the Congo (DRC) (Ref. 14). During the epidemic, a mortality rate of 60 to 80 percent was reported among hospital cases. After an incubation period of approximately 7 days, the early clinical features of the disease included fever, headache, sore throat, diarrhea and myalgias, followed by vomiting, worsening diarrhea, oliguria, shock and death after 7 to 14 days. In May of 1995, the month of peak onset of new cases, the DRC requested international assistance in investigating the cause of the outbreak. Laboratory testing by the Centers for Disease Control and Prevention (CDC) confirmed the presence of the Zaire subtype of Ebola hemorrhagic fever. Continued investigation and testing enabled the international team to identify modes of transmission and to specify the precautions necessary to prevent further spread of the virus. According to the CDC, prompt laboratory diagnosis is an essential component of the surveillance needed to maximize Ebola prevention and control measures (Ref. 15). In this instance, the lack of early detection and proper management of Ebola hemorrhagic fever patients resulted in numerous deaths among both health care personnel and patients (Rollin and Ksiazek, 1998). By hastening the disclosure of important risk information, the proposed rule would assist public health agencies and health care providers in more rapidly identifying and controlling any zoonotic viruses that might emerge following xenotransplantation.

As of April 1999, the United Network for Organ Sharing (UNOS) reported a total of 62,443 patients on the waiting list for an organ transplant. This number far exceeds the total of approximately 20,000 transplants performed each year (Ref. 16). In addition to bolstering the supply of viable organ transplants, patients may also benefit from cellular and tissue therapies involving a xenotransplantation product. Although the potential to fill unmet needs is great, the number of prospective xenotransplant recipients represents a sizeable population at potential risk of zoonotic infection. The proposed data disclosures would help to provide the information needed by the public to understand, manage, and minimize the risks associated with these advancing medical technologies.

D. Impact on Small Entities

The agency has only limited information to estimate the number of small entities conducting clinical investigations of human gene therapy or xenotransplantation. As indicated in the cost analysis, the overall number of business entities sponsoring clinical trials is estimated to be 147. Although a few companies are a part of larger firms, many others may have annual revenues of less than $5 million, which is the revenue level that identifies a small business, according to the Small Business Administration. The estimated cost impact of $843 per sponsor per year reflects the staff time that would need to be allocated to produce redacted versions of the specified documents for the purpose of public disclosure.

The proposed rule offers sponsors considerable flexibility in implementation by allowing for a range of approaches for preparing a redacted version. Under the proposed rule, acceptable approaches range from submitting a ''marked up'' version of the original that simply obscures the information not to be disclosed, to development of a separate document that abstracts the needed information for the public from the original unabridged version submitted to FDA. This flexibility will help to minimize the cost impact.

The agency does not anticipate that the estimated cost will significantly burden any of the sponsors. However, because of the limited information available for establishments sponsoring clinical trials in human gene therapy and xenotransplantation, and its importance in developing estimates of the small entity impact, the agency requests detailed comment on the number and type of businesses sponsoring clinical trials in human gene therapy or xenotransplantation, and the expected impact of the proposed requirements on these entities.

In developing the proposed rule, the agency considered but rejected two alternatives that might impose less burden on small businesses. The agency found, however, that these alternatives would be less effective in supporting the advancement of this research, because of unanswered concerns regarding patient safety and public health. One of the alternatives considered involved voluntary disclosure by clinical trial sponsors without a regulatory requirement. This alternative would reduce costs to industry only if establishments failed to voluntarily provide the needed information for disclosure. Moreover, while voluntary provision of this information would be no less burdensome for industry, it could prove inadequate in protecting public health, because the agency would have no means of assuring the quality and consistency of the content of the voluntarily disclosed information, or the timeliness of its reporting. The disclosure of timely, accurate, and complete information is critical to an appropriate agency response to adverse outcomes, including the emergence of novel and potentially life-threatening infectious agents, or the alteration of the germline in patients participating in the clinical study. Also, voluntary disclosure provides no means for the agency to ensure a balanced dissemination of information on identified risks and benefits. Such balance is central to an adequate public understanding of the technologies, and to an informed public discussion of the overall risk versus benefit to patients and communities.

A second alternative to the proposed rule would require disclosure, but would have FDA assume the sole responsibility for redaction of documents submitted by the sponsor. Although this alternative would reduce the direct cost impact for sponsors, the limited number of agency staff available to perform this task would introduce the risk of delay in producing the redacted

version for public disclosure. This outcome could potentially result in delaying the research, or delaying the timely public availability of critical information.

VI. References

The following references have been placed on display in the Dockets Management Branch and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Eastland, T., ''Infectious disease transmission through cell, tissue and organ transplantation: reducing the risk through donor selection,'' *Cell Transplantation* vol 4. pp. 455–477, 1995.
2. Delmonico, F. L. and D. R. Snydman, ''Organ donor screening for infectious diseases'' *Transplantation*, vol. 65, pp. 603–610, 1998.
3. Regamey, N., M. Tamm, M. Wernil, A. Witschi, G. Thiel, G. Cathomas, and P. Erb, ''Tranmission of human herpesvirus 8 infection from renal-transplant donors to recipients.'' *New England Journal of Medicine*, vol. 339, pp.1358–1363, 1998.
4. ''Guidelines for Research Involving Recombinant DNA Molecules,'' Appendix M–Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (PTC), http://www4.od.nih.gov/oba/guidelines.html.
5. Friedmann, T., ''Overcoming the Obstacles to Gene Therapy,'' *Scientific American*, vol. 276, No. 6, pp. 96–101, June 1997.
6. Haberman, R. P., T. J. McCown, and R. J. Samulski, ''Inducible Long-Term Gene Expression in Brain With Adeno-Associated Virus Gene Transfer,'' *Gene Therapy*, vol. 5, No. 12, pp. 1604–1611, December 1998.
7. Middleton, P. G. and E. W. F. W. Alton, ''Gene Therapy for Cystic Fibrosis: Which Postman, Which Box?'' *Thorax*, vol. 53, No. 3, pp. 197–199, March 1998.
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9. Yang, E.Y., D. L. Cass, K. G. Sylvester, J. M. Wilson, and N. S. Adzick, ''Fetal Gene Therapy: Efficacy, Toxicity, and Immunologic Effects of Early Gestation Recombinant Adenovirus,'' *Journal of Pediatric Surgery*, vol. 34, No. 2, pp. 235–241, February 1999.
10. *Report of WHO Consultation on Xenotransplantation*, World Health Organization, Emerging and other Communicable Diseases Surveillance and Control, Geneva, Switzerland, pp. 28–30, October 1997.
11. Van der Laan, L. J., C. Lockey, B. C. Griffeth, F. S. Frasier, C. A. Wilson, D. E. Onions, B. J. Hering, Z. Long, E. Otto, B. E. Torbett, D. R. Salomon, ''Infection by Porcine Endogenous Retrovirus After Islet Xenotransplantation in SCID Mice,'' *Nature*, vol. 407 (6800), pp. 90–94, September 7, 2000.
12. U.S. Department of Health and Human Services, Centers for Disease Control, ''Outbreak of Hendra-Like Virus—Malaysia and Singapore, 1998–1999,'' *Morbidity and Mortality Weekly Report*, vol. 48, No. 13, April 9, 1999.
13. Rollin, P. E. and T. G. Ksiazek, ''Ebola Haemorrhagic Fever,'' *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 92, pp. 1–2, 1998.
14. Roels, T. H., A. S. Bloom, J. Buffington, G. L. Muhumgu, W. R. MacKenzie, A. S. Khan, R. Ndambi, D. L. Noah, H. R. Rolka, C. J. Peters, and T. G. Ksiazek, ''Ebola Hemorrhagic Fever, Kikwit, Democratic Republic of the Congo, 1995: Risk Factors for Patients with a Reported Exposure,'' *The Journal of Infectious Diseases*, vol. 179 Supplement 1:S92–97, 1999.
15. Centers for Disease Control, ''Update: Outbreak of Ebola Viral Hemorrhagic Fever—Zaire 1995,'' *Journal of the American Medical Association*, vol. 274, No. 5, August 1995.
16. *U.S. Facts About Transplantation*, UNOS, (c) 1998, http://www.unos.org/newsroom/critdata_main.htm.

VII. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have a practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation.

Description: FDA is proposing new regulations to require that sponsors of IND's involving human gene therapy or xenotransplantation submit information related to the IND in redacted version for public disclosure, removing all information that would be defined as trade secret or personal information whose disclosure would constitute a clearly unwarranted invasion of privacy, and certain confidential commercial information. Each submission for public disclosure would be accompanied by a statement, signed by a responsible person, that the information has been suitably redacted. FDA would then publicly disclose the redacted version to provide an opportunity for public education, discussion, and consideration of public health and safety issues, as well as consideration of societal and ethical issues.

FDA is also proposing to require that the sponsor submit any copyrighted material in a single appendix to each redacted version and any copyrighted material whose copyright is not owned by the sponsor not be included in any other section of the redacted version. The proposal would further require that the redacted version include a bibliography of the copyrighted material contained in the appendix. This provision would facilitate the timely public disclosure of the redacted version on the Internet, with the copyrighted information excluded. Making available copyrighted material on the Internet is not considered ''fair use'' of copyrighted material.

Description of Respondents: Sponsors of clinical investigations involving human gene therapy or xenotransplantation.

FDA has estimated the burden for each provision that describes a collection of information. The estimates are based on FDA's experience in reviewing IND submissions and in redacting documents related to an IND.

Under proposed § 601.53(b), approximately 147 sponsors of clinical investigations involving human gene therapy (134 sponsors) and xenotransplantation (13 sponsors) would be required to submit a redacted version of certain documents under the IND. For all 147 sponsors, these documents include the original IND (45 submissions/year), amendments to an IND (270 submissions/year), IND safety reports (90 submissions/year), and annual reports (100 submissions/year) for an estimated total of 505 submissions/year (45 + 270 + 90 + 100). FDA has estimated the time necessary to copy and redact each of the above types of submissions; i.e., IND submission, 24 hours/submission; amendments, .5 hour/per submission; IND safety reports, .5 hour/submission; and annual reports, 20 hours/submission. The total burden equals the sum of the burdens estimated for each type of submission (45x24 +

270x.5 + 90x.5 + 100x20 equals 3,260 hours).

Under § 601.53(c) all submissions under § 601.53(b) must be readily separable from the original submission and clearly marked on each page as suitable for disclosure. Under § 601.53(d) of the proposed rule, sponsors of human gene theraphy and xenotransplantation clinical studies would be required to submit copyrighted material in a single appendix to each redacted submission and include in the redacted version a bibliography of these materials. The hours per response, therefore, are an average estimate of the total time for redaction of the document, separation of copyrighted material and preparation of a bibliography, marking of each page as suitable for public disclosure, and submission to FDA, as provided in § 601.53(b), (c), and (d). The information collection burdens associated with the submission of an IND as provided in part 312 are approved by OMB under OMB control number 0910–0014.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.53(b), (c), and (d)	147	3.4	505	6.5	3,282

[1] There are no capital costs and maintenance costs associated with this collection of information.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), FDA has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons may submit comments on the information collection requirements of this proposal by February 20, 2001, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

VIII. Proposed Effective Dates

FDA proposes that any final rule that may issue based on this proposal become effective 90 days after the date of its publication in the **Federal Register**. On or after that date, sponsors of human gene therapy or xenotransplantation clinical trials would be required to submit a redacted version of the data and information specified in the final rule as part of a submission into an IND. Sponsors may voluntarily submit a redacted version immediately upon the date of issuance of the final rule. FDA is proposing, for sponsors of xenotransplantation clinical trials who have submitted an IND prior to the effective date of the final rule, that the sponsor submit for public disclosure a redacted version of the information held under the IND, to contain the information specified in proposed § 601.52. FDA invites comment on the length of time after issuance of the final rule that these sponsors should be provided to submit the redacted information.

IX. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this proposal by April 18, 2001. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Submit written comments on the information collection provisions by February 20, 2001. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 20, 312, and 601 be amended as follows:

PART 20—PUBLIC INFORMATION

1. The authority citation for part 20 continues to read as follows:

Authority: 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393, 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1.

2. Section 20.100 is amended by adding paragraph (c)(43) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(43) Data and information submitted related to human gene therapy or xenotransplantation, in § 601.52 of this chapter.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

4. Section 312.42 is amended by adding paragraph (b)(7) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(7) *Clinical hold of any investigation, as defined in § 601.52 of this chapter, involving human gene therapy or xenotransplantation.* FDA may place a proposed or ongoing investigation, as defined in § 601.52 of this chapter, involving human gene therapy or xenotransplantation on clinical hold if it is determined that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) The sponsor has not submitted a redacted version of the data and information, as specified in § 601.52 of this chapter, for public disclosure that complies with the requirements of § 601.53 of this chapter.

* * * * *

5. Section 312.130 is amended by revising paragraph (b) to read as follows:

§ 312.130 Availability for public disclosure of data and information in an IND.

* * * * *

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug or antibiotic drug will be handled in accordance with the provisions established in § 314.430 of

this chapter for the confidentiality of data and information in applications submitted in part 314 of this chapter. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§ 601.50, 601.51, and 601.52 of this chapter.

* * * * *

PART 601—LICENSING

6. The authority citation for part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

7. Section 601.50 is amended by revising the section heading and paragraph (a) to read as follows:

§ 601.50 Confidentiality of data and information in an investigational new drug application for a biological product.

(a) Except as provided in § 601.52, the existence of an IND application for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

* * * * *

8. Section 601.51 is amended by revising the section heading and paragraph (a) to read as follows:

§ 601.51 Confidentiality of data and information in a biologics license application.

(a) For purposes of this section the *biological product file* includes all data and information submitted with or incorporated by reference in any biologics license application, IND's incorporated in any such application, master files, and other related submissions. Except as provided in § 601.52, the availability for public disclosure of any record in the biological product file shall be handled in accordance with the provisions of this section.

* * * * *

9. Section 601.52 is added to subpart F to read as follows:

§ 601.52 Availability for public disclosure of certain data and information related to an IND concerning human gene therapy or xenotransplantation.

(a) *Definitions*. The following definitions of terms apply to this section:

(1) *Human gene therapy* means the administration of genetic material in order to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use. Cells may be modified ex vivo for subsequent administration or altered in vivo by gene therapy products given directly to the subject.

(2) *Xenotransplantation* means any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: Live cells, tissues, or organs from a nonhuman animal source; or human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

(b) *Scope*. Except as otherwise provided in this section, the availability for public disclosure of data and information related to human gene therapy or xenotransplantation shall be in accordance with §§ 601.50 and 601.51.

(c) *Information for public disclosure*. FDA will make available for public disclosure the following types of data and information related to an IND concerning human gene therapy or xenotransplantation. Names and other personal identifiers of patients and, except as specifically provided in this section, names and personal identifiers of and third party, such as physicians or hospitals, will not be made available for public disclosure.

(1) Product and patient safety data and related information. For purposes of this section product and patient safety data and related information include results of preclinical and clinical studies and tests that demonstrate the safety and/or feasibility of the proposed procedures. This may include, but is not necessarily limited to, analysis in animals, humans, or in vitro systems of gene transfer, expression, and persistence; vector biodistribution; evidence for immune response/anergy; biological activity; and results of product safety testing including testing for known xenogeneic and human infectious agents and replication competent virus; and qualification of source herd, individual source animal, and source organ/tissue/cells for xenotransplantation in humans. Also included is information on monitoring or prevention of potential health risks to the recipient, close contacts, and health care workers, such as patient monitoring for replication competent retrovirus and viral shedding and measures taken to prevent transmission of infectious disease. The availability for public disclosure of data and information in an IND safety report or annual report, as provided under §§ 312.32 and 312.33 of this chapter, will be governed by the provisions of paragraphs (c)(7) and (c)(8) of this section.

(2) The name and address of the sponsor.

(3) The clinical indications to be studied.

(4) A protocol for each planned study, to include:

(i) A scientific abstract and a nontechnical abstract.

(ii) A statement of the objectives, purpose, and rationale of the study.

(iii) The name and address of each investigator.

(iv) The name and address of the official contacts of each local review body as appropriate (Institutional Review Board, Institutional Biosafety Committee) and the dated copies of each committee's approval of the study.

(v) The criteria for patient selection and exclusion and an estimate of the number of patients to be studied.

(vi) A description of the treatment that will be administered to patients and the clinical procedures, laboratory tests, or other measures to be taken to monitor the safety and effects of the drug in human subjects and to minimize risk.

(5) Written informed consent form(s) as provided in § 50.27 of this chapter.

(6) Identification of the biological product(s) and a general description of the method of production, including a description of product features that may affect patient safety. The information shall include, as applicable, the vector name and type; gene insert; regulatory elements and their source; intended target cells; source of cells, tissues, or organ(s); method used to prepare the vector containing cells; method used to procure and prepare cells, tissues, or organs for xenotransplantation; purity of cells; adventitious agent testing; description of the delivery system; ancillary products used during production; herd colony and individual source animal health maintenance and surveillance records; and biological specimens to be archived from source animals.

(7) IND safety reports, as provided in § 312.32 of this chapter, and other similar data and information.

(8) Information submitted in the annual report to include, as applicable, assessment of evidence of gene transfer, gene expression in target cells, biological activity, immune response, status of autopsy request and evidence of gene transfer and gonadal distribution upon autopsy, results from assessment for evidence of infection by agents associated with the product, adverse experiences, and a list of subjects who died during participation in the investigation, with the cause of death for each subject.

(9) The regulatory status of the IND, such as on hold, in effect, inactive, or

withdrawn, the dates of these actions, and the reasons for these actions.

(10) Other relevant data and information that the Director, CBER, determines are necessary for the appropriate consideration of the public health and scientific issues, including relevant ethical issues, raised by human gene therapy or xenotransplantation.

10. Section 601.53 is added to subpart F to read as follows:

§ 601.53 Submission of certain data and information related to human gene therapy or xenotransplantation for public disclosure.

(a) A sponsor of an IND shall submit to FDA for public disclosure in a redacted version the submissions identified in paragraphs (b)(1) through (b)(5) of this section. Each submission shall include all applicable information identified as disclosable in § 601.52, but shall be redacted to remove or obscure all information considered confidential as a trade secret, certain confidential commercial information, such as information regarding commercial licensing agreements or the identification of suppliers, and names and other personal identifiers of patients and, except as specifically provided in this section, names and personal identifiers of any third party, such as physicians or hospitals, must be redacted.

(b) The following shall be submitted in a suitably redacted version and in duplicate at the time points noted:

(1) Information as defined under § 601.52 at the time of initial IND submission.

(2) Any amendment documenting changes or additions to the information as defined under § 601.52 at the time the amendment goes into effect.

(3) IND safety reports at the time of submission of the initial report to FDA.

(4) The annual report, within 60 days of the anniversary date that the IND went into effect, in accordance with § 312.33 of this chapter.

(5) Other information upon the specific request of the Director, CBER.

(c) The submissions identified in paragraph (b) of this section shall be submitted in a form readily separable from the original unabridged submission to FDA and clearly marked on each page of the redacted version as suitable for public disclosure.

(d) Any copies of copyrighted material shall be submitted in a single appendix to each redacted version. Copyrighted materials whose copyright is not owned by the applicant shall not be included in any other section of the redacted versions. A bibliography of copyrighted materials contained in the appendix shall be included as part of each redacted version.

(e) Any data or information submitted to FDA as a redacted version for public disclosure in accordance with paragraph (a) of this section shall be accompanied by the following statement signed by a responsible individual:

The information contained herein has been redacted for public disclosure. The only material removed from these records is: Confidential commercial or trade secret information exempt from disclosure under the Freedom of Information Act (5 U.S.C. 552 (b)(4)) and the Food and Drug Administration's implementing regulations (21 CFR 20.61); names and other personal identifiers of patients and, except as specifically provided in the regulations, names and other personal identifiers of any third party.

I declare, under the penalty of perjury, that the foregoing is true and correct.

Dated: December 20, 2000.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 01–1048 Filed 1–17–01; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 192 and 592

[Docket No. 00N–1396]

RIN 0910–AC15

Premarket Notice Concerning Bioengineered Foods

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the submission to the agency of data and information regarding plant-derived bioengineered foods that would be consumed by humans or animals. FDA is proposing that this submission be made at least 120 days prior to the commercial distribution of such foods. FDA is taking this action to ensure that it has the appropriate amount of information about bioengineered foods to help to ensure that all market entry decisions by the industry are made consistently and in full compliance with the law. The proposed action will permit the agency to assess on an ongoing basis whether plant-derived bioengineered foods comply with the standards of the Federal Food, Drug, and Cosmetic Act (the act).

DATES: Submit written comments on the proposed rule by April 3, 2001. Submit written comments on the information collection provisions by February 20, 2001.

See section XIV of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Regarding human food issues: Linda S. Kahl, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3101.

Regarding animal feed issues: William D. Price, Center for Veterinary Medicine (CVM) (HFV–200), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6652.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background
A. The 1992 Policy
B. Consultations Under the 1992 Policy and the 1996 Procedures
C. Public Meetings
II. Legal Authority
III. Scope
IV. Definitions
V. Requirement for Premarket Biotechnology Notice
A. Foods That Are Subject to the Requirement
B. Origin of Data and Information
C. Timing
VI. Recommendation for Presubmission Consultation
A. Presubmission Consultation Program
B. Public Disclosure
C. Standard Procedures
VII. Premarket Biotechnology Notice: Administrative Information
A. Submissions to CFSAN for Use in Human Food, Animal Feed, or Both
B. Paper Copies
C. Electronic Copies
D. English Language Translations, Incorporation by Reference, and Available Guidance Documents
E. Opportunity to Withdraw
VIII. Premarket Biotechnology Notice: Required Parts
A. Part I: Letter