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Appendices

Various authors

APPENDICES

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APPENDIX A

U.S. Food and Drug Administration

FDA's Vision

FDA in the year 2000 will be ...

* A strong science-based agency—to accurately detect and assess health risks, and to set appropriate standards.

* A trusted agency—to enforce the Food, Drug, and Cosmetic Act fairly, uphold safety standards, and protect consumers.

* An enabling agency—to steward needed products and to promote public health.

* A collaborative agency—to strengthen ties to scientific, health provider, and regulatory communities both domestically and internationally.

* A high-performance agency—to capitalize on state-of-the-art information and communication technologies and management systems to enhance performance.

* An employee-valued agency—to recruit, develop and advance employees equitably, and to position the agency to meet the changing work force needs of the 21st century.

FDA principally serves the general public in its health and safety mission. FDA also recognizes its responsibilities to the industries that it regulates and will work with them in shepherding new technologies to the marketplace. Thus it strives to maximize public health protection while minimizing regulatory burden.

APPENDIX B

(U.S. Food and Drug Administration)

REINVENTING THE REGULATION OF DRUGS MADE FROM BIOTECHNOLOGY

President Bill Clinton
Vice President Al Gore

National Performance Review
November 1995

OVERVIEW

INTRODUCTION

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

Today's report focuses on FDA's efforts to reform the regulation of biotech drugs used for therapy. The changes outlined in this report represent the most significant overhaul of the regulation of biotech drugs the FDA has ever attempted. FDA will in essence harmonize its regulation of biotech drugs that qualify as "well-characterized," making uniform the requirements of its two product centers responsible for helping to ensure the safety and effectiveness of biologic drugs: the Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER). According to the biotechnology industry, these changes will save their companies millions of dollars and cut drug development time by months. At the same time, the agency believes that these modifications will not diminish the safety and effectiveness of biotech drugs.

For well-characterized, therapeutic biotechnology-derived drugs—a definition that includes most biotech drugs—FDA will:

* eliminate CBER's existing requirement that manufacturing facilities be separately licensed;

* eliminate the existing policy under which CBER evaluates and releases individual lots of biotech drugs after the drugs have been approved; and

* replace with one form the 21 different approval application forms for biotech drugs, blood, vaccines, and other drugs.

For all biologics, including biotech drugs regulated by CBER, FDA will:

* eliminate the current requirement that promotional labeling be approved prior to the launch of a biologic and for 120 days following its approval;

* decide within 30 days whether newly submitted information supports the initiation or continuation of a human investigation that the agency has put on hold; and

* permit a corporation to designate more than one person to act as a "Responsible Head" in dealings with CBER.

These and other initiatives described in this report will greatly streamline the regulation of biotech drugs, harmonize the requirements with respect to manufacturing, and facilitate the development and marketing of new biotech drugs.

BACKGROUND

Two FDA operating components regulate drugs: CBER, which regulates blood, vaccines, human tissues and many drugs derived from living organisms, principally under the Public Health Service Act, and CDER, which regulates other drugs under the Federal Food, Drug, and Cosmetic Act.

The drugs made from living organisms regulated by CBER are subject to statutory requirements in addition to those governing all other drugs. For statutory reasons, and historical reasons, the two centers have approached the regulation of biotech drugs somewhat differently. For example, CBER has required two separate licenses for every biotech drug that it regulates: (1) a product license; and (2) an establishment license for each facility in which the drug is manufactured. CBER has also required "lot-by-lot release" for the biotech drugs that it regulates, which means that CBER authorizes the release of individual lots.

The agency is now proposing to harmonize the two centers' policies and requirements for therapeutic biotech drugs that qualify as "well-characterized," which includes most biotech drugs.

FDA'S PROPOSALS FOR REFORM

Elimination of the Requirement for an Establishment License Application for Most Biotech Drugs

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

Technical advances over the last 15 years have greatly increased scientists' ability to control the manufacture of many biotech drugs. After over a decade of experience with these drugs, the agency has found that it can review the safety, purity, potency, and effectiveness of most biotech drugs regulated by CBER without requiring a separate establishment license.

Proposal: CBER will eliminate the requirement for submission and approval of establishment license applications for therapeutic biotech drugs that are "well-characterized." In place of the establishment license application, CBER will evaluate the adequacy of manufacturing facilities by inspection for compliance with good manufacturing practices and through the use of a new chemistry, manufacturing, and controls section of a newly revised product license application. The format and content of the product license application will be harmonized with a slightly revised new drug application for the well-characterized biotech drugs regulated by CDER. (The new drug application revision will consist of the addition of a simple one-page floor plan sufficient to allow an FDA reviewer to visualize the production of the drug, but will not require a detailed description of equipment placement.) CDER and CBER will use the same technical guidance documents.

The harmonization across centers of the chemistry, manufacturing, and controls format and content will also reduce the amount of information that biotech companies will need to provide in the product license application. For example, in many instances manufacturing facility information will not be submitted to the agency, but will be reviewed during good manufacturing practice inspections.

Preapproval inspections for biotech drugs regulated by CBER will continue to be done jointly by headquarters and field staff. These inspections will be comparable to the inspections currently conducted for biotech drugs regulated by CDER. To ensure that inspection procedures for biotech drugs

will be consistent across the centers and the field, the FDA will train its scientists and inspectors using the same principles.

As described in the National Performance Review's report on Reinventing Drug and Medical Device Regulations, FDA has already begun reducing requirements for preapproval of manufacturing and site changes. Under this proposal, manufacturing and site change requirements for biotech drugs will be harmonized across CBER and CDER. To implement this proposal, the agency will develop a definition of "well-characterized" biotech drugs. The agency anticipates that most therapeutic biotech drugs regulated by CBER will fall within this definition and, therefore, will be exempted from the requirement to submit and have approved a separate establishment license application. To refine the agency's definition of well-characterized biotechnology-derived biologic drugs eligible for these streamlining efforts, FDA is also sponsoring a public scientific workshop on Dec. 11-13, 1995.

The agency anticipates that the workshop may identify additional product classes that could be exempted from the establishment license application requirements.

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

Impact: Companies developing and manufacturing most biotech drugs regulated by CBER will no longer have to prepare establishment license applications and submit them to the agency for approval. The amount of information that companies will need to provide in the product license application will also be reduced. These proposed changes will get biotech drugs to market faster and will enable companies to devote more resources to developing drugs and ensuring that they are manufactured appropriately, and fewer resources to submitting documentation to the agency. This change will especially benefit small biotechnology companies that lack experience in preparing establishment and product license applications. According to companies, the establishment license application requirement adds substantially to the cost of biotech drug approval.

These proposed changes will also harmonize the requirements across the agency concerning a company's ability to contract out manufacture of its well-characterized therapeutic biotech drugs. These proposals will eliminate the requirement that each separate contract facility engaging in significant production steps obtain its own establishment license. Instead, each such biotech drug will be covered by only one marketing application, which lists all manufacturing locations, regardless of how many separate companies are involved in its manufacture.

Implementation and Timeline: Within 30 days, the agency will issue a proposed rule under which companies manufacturing "well-characterized

biotechnology-derived drugs" would not be required to obtain a separate establishment license. The proposal will include a definition of "well-characterized biotechnology-derived drugs," and will allow 30 days for comment. The agency will publish a final rule 60 days after the close of the comment period.

Elimination of Lot Release Requirements for Biotech Drugs

Background: Biologics have traditionally been complex mixtures of substances produced primarily from living organisms, and have been difficult to define by precise tests. They include vaccines, products made from human or animal blood, and other products made from a variety of materials. Because of the inherent variability of these products, each individual lot of most biologics has been subject to evaluation and testing by FDA.

Historically, the lot release requirement has served an important role in the regulation of biological drugs and has prevented the distribution of unacceptable lots. Greater control has been achieved by manufacturers over the production of biotech drugs through in-process controls, process validation, and recent advances in analytical techniques. For well-characterized therapeutic biotech drugs, the agency has found that once a company has demonstrated its ability to consistently produce acceptable lots, and has procedures in place that will prevent the release of lots that do not meet release specifications, it is not necessary for FDA to verify that each manufactured lot is acceptable for release.

Proposal and Justification: Once a well-characterized therapeutic biotech drug has been licensed for marketing and its manufacturing process has been validated, it will not be subject to lot-by-lot release by FDA. The agency will monitor companies' compliance with the requirement that they assay each lot and release only those that meet release specifications. In light of the developments in manufacturing and testing for well-characterized biotech drugs, FDA's lot-by-lot release is not necessary.

Impact: The elimination of lot-by-lot release of biotech drugs will result in a significant savings of time and resources for both the industry and the agency. There will be no significant additional risk to public health because these drugs are well-characterized and do not warrant direct agency participation in quality-assurance testing.

Implementation and Timeline: The agency will immediately begin sending letters to affected companies advising them of the change in the lot-by-lot release policy. Within 30 days, the agency will issue a notice describing the elimination of lot-by-lot release for well-characterized therapeutic biotech drugs.

Harmonized Application Format for All Drugs and Biologics

Background: CBER currently uses 19 different product license application forms and a separate establishment license application form. In addition,

CDER has a separate new drug application form. This is confusing for the industry.

Proposal and Justification: The agency will consolidate the 21 different application forms into one. The harmonized form will contain a technical section on the establishment, which will be applicable only to those biologics for which establishment application review will continue to be necessary. The agency also intends to include some elements from the European Community format in order to facilitate international harmonization of applications.

In addition to a harmonized application form, the technical requirements and guidance documents will be the same across the agency for well-characterized therapeutic biotech drugs, regardless of which center regulates them. Also, the agency will harmonize its procedures regarding contracting out manufacture of drugs and biologics.

Impact: Companies will be able to provide higher quality submissions. Time to prepare applications will be reduced because forms will be standardized.

FDA will reduce 21 applications to one application. The standard format should expedite review by FDA staff and can be used as a basis for electronic submissions.

Implementation and Timeline: Within 60 days, CBER will make available a draft form which companies may choose to use for product license applications for well-characterized therapeutic biotech drugs. Within six months, FDA will publish a proposed revised application form for all drugs and biologics.

Elimination of the Preapproval Requirement for Promotional Labeling

Background: CBER currently requires preapproval of promotional labeling prior to launch of a new biologic and for 120 days following approval of a new biologic. This is inconsistent with what is required by CDER, which requires companies to send such information to the agency at the time the company disseminates it.

Proposal and Justification: CBER will change its current policy that labeling in connection with the launch of a new product be approved.
Impact: Industry will no longer need to await approval of promotional labeling prior to disseminating it. Agency resources will be freed up to accomplish other review activities.

Implementation and Timeline: Effective immediately, the agency will no longer require preapproval of promotional labeling. The agency will promptly issue a Federal Register notice announcing this new policy.

Agency Responses to Data Submitted Regarding Clinical Holds

Background: Companies or individuals that intend to study investigational drugs or biologics in humans must first submit an investigational new drug (IND) application to the agency. They may proceed with the study 30 days

after the agency receives the application, unless FDA puts the study on clinical hold. A clinical hold is a directive issued by FDA that prevents the clinical study from proceeding. Thus, a researcher or company that intends to begin testing a new biologic in humans, or is in the process of testing a new biologic in humans, may not begin or continue the study until FDA releases the clinical hold. Currently, FDA has no internal requirements regarding how much time it may take to evaluate data submitted by the sponsor in response to the clinical hold. While the agency has generally responded in a timely manner, sponsors would like the predictability engendered by an agency commitment to respond within a specified time frame.

Proposal and Justification: FDA will commit itself to review and respond to data submitted in response to a clinical hold within 30 days of receiving the submission. Unless FDA responds within that period, the investigation may proceed. FDA believes that the 30-day period will meet the needs of sponsors, and is within the resource capabilities of the agency.

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

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

Revision of the Requirements for a Responsible Head for Biological Establishments

Background: Manufacturers of biological products are required to name a "Responsible Head" who is to exercise control of the manufacturing establishment in all matters relating to compliance with the regulations and who is to represent the manufacturer in all dealings with FDA. This individual must have an understanding of the scientific principles and techniques related to the manufacture of biological products.

In the past, biological product manufacturers typically were small companies, such as blood banks, that made products at one location. The requirement that a single responsible head represent the company was practical for such small operations. Today, however, manufacturers of biological products tend to be larger firms with more manufacturing locations and more complex corporate structures. Most companies do not have one person with the knowledge to represent a company in all matters, but instead have several people with expertise in regulatory affairs, manufacturing, and medical issues.

Proposal and Justification: FDA proposes to revise its requirements for a "Responsible Head" to allow more flexibility to assign control and oversight responsibility within a company. The revisions will still ensure the proper oversight and accountability within a firm, but will conform to the way biological firms assign responsibilities to their senior experts.

Impact: Firms will be able to divide management responsibility among appropriate regulatory, medical, or manufacturing staff. These individuals will be able to directly communicate with the agency on official matters related to biological products they manufacture.

Implementation and Timeline: FDA will publish a proposal to revise the regulation within nine months.

(U.S. Food and Drug Administration)

(What's New)

Here are links to new items FDA has made available on its Internet site during the past four weeks. Also check the FDA News page for additional new information, including press releases, Congressional testimony, and other public statements.

Approval of New Drugs in the United States Comparison With the United Kingdom, Germany and Japan. David A. Kessler MD, JD; Arthur E. Hass; Karyn L. Feiden; Murray Lumpkin, MD; Robert Temple, MD. Originally published in Journal of the American Medical Association, December 11, 1996 - Vol 276, No. 22

Latest Major Speech: David A. Kessler, M.D., Commissioner of Food and Drugs—Annual Meeting, Food and Drug Law Institute (Dec. 10, 1996) Pesticide Residue Monitoring Program Report for 1995

A summary of the results of FDA's pesticide residue monitoring program for the period Oct. 1, 1994, through Sept. 30, 1995. Selected findings from the Total Diet Study are also presented.

FDA's Office of Women's Health Web Site

Important information for and about women from FDA and other sources.

Protection of Human Subjects; Informed Consent Verification—Final Rule (Nov. 5, 1996)

Protection of Human Subjects; Informed Consent—Final Rule (Oct. 2, 1996)

What's New at the Center for Devices and Radiological Health

What's New at the Center for Drug Evaluation and Research

What's New at the Center for Veterinary Medicine

(Comments) (FDA Home Page)

Last revised Dec. 16, 1996

APPENDIX C

A Guide to Helpful Government Documents on the Internet

Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

..... map available on page 134

Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

..... map available on page 135

Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1994) [PTC MAB.TXT; PTC MAB.W51]

..... map available on page 136

Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived From Transgenic Animals [PTC TGA.TXT; PTC TGA.W51]

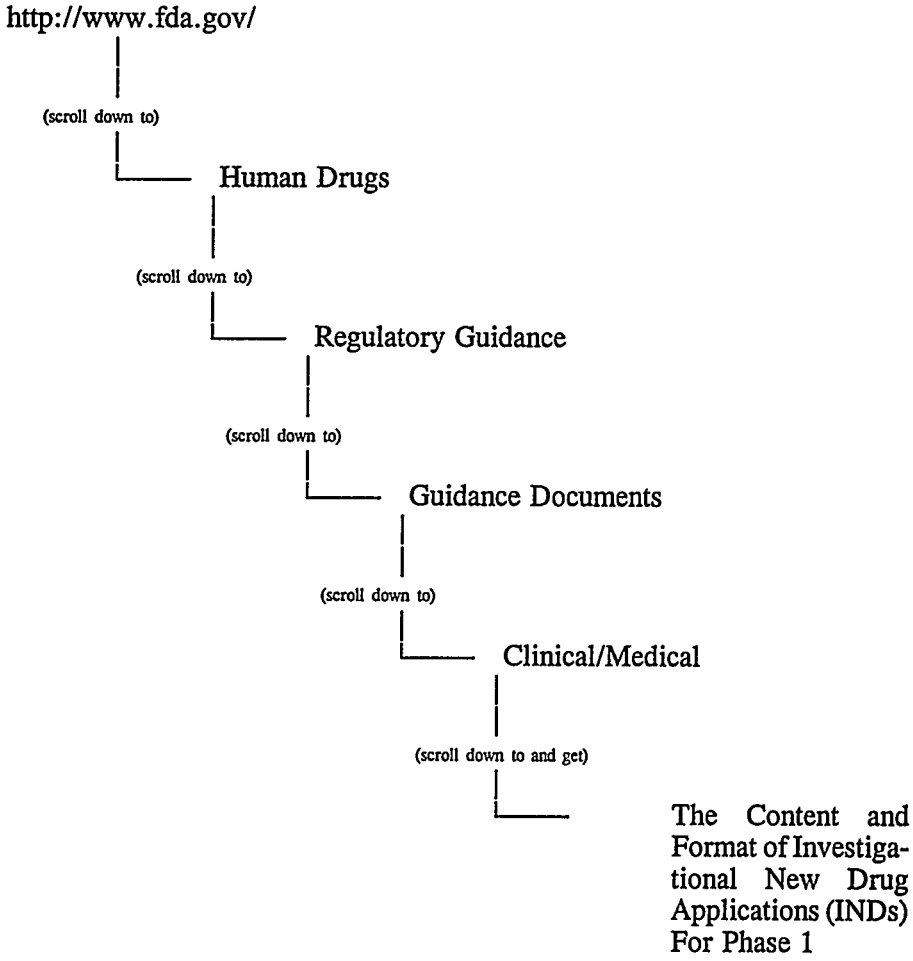
..... map available on page 136

Addendum to the Points to Consider in Human Somatic and Gene Therapy (1991) [GSTA.TXT; GSTA.W51]

..... map available on page 136

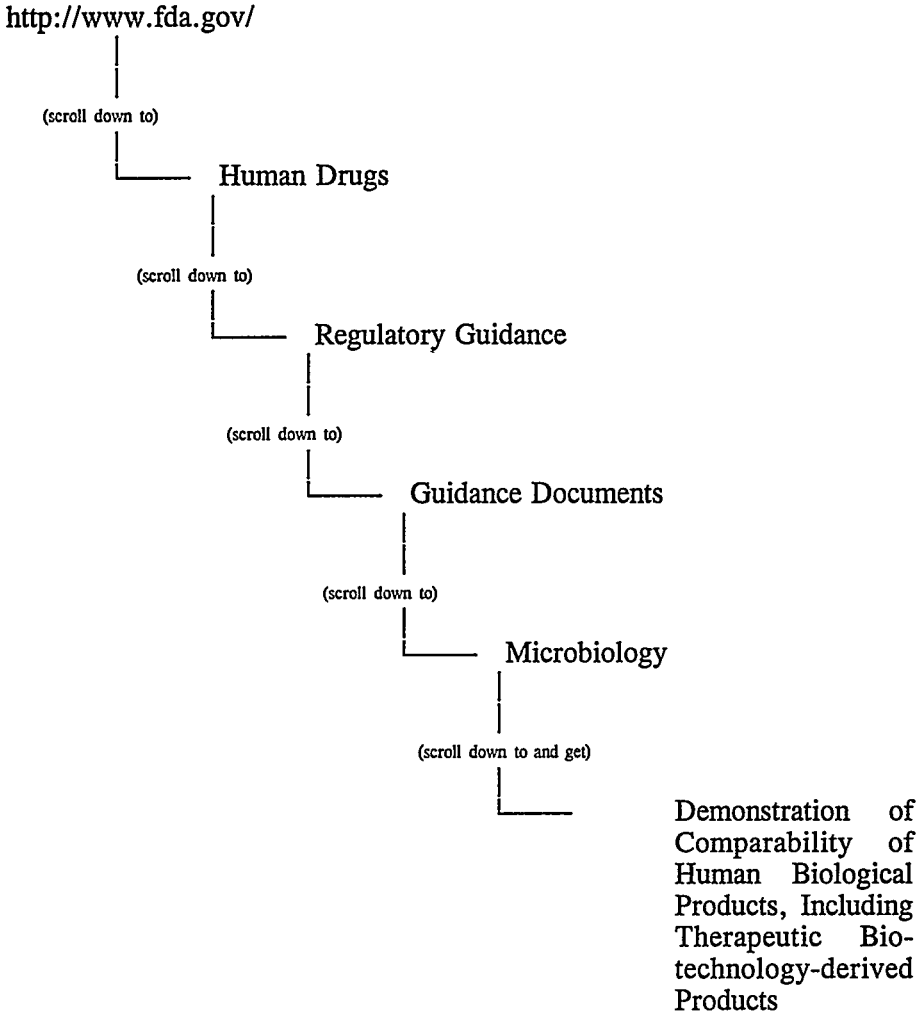
Map of how to access document on the Internet:

Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products:



Map of how to access document on the Internet:

Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

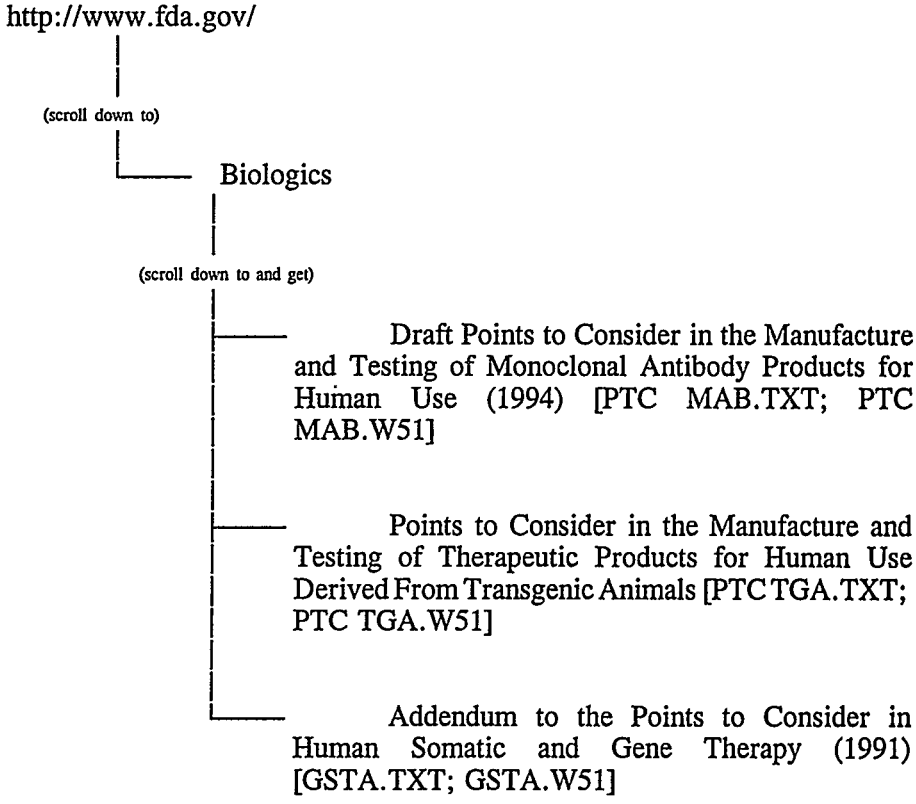


Map of how to access document on the Internet:

Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1994) [PTC MAB.TXT; PTC MAB.W51]

Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived From Transgenic Animals [PTC TGA.TXT; PTC TGA.W51]

Addendum to the Points to Consider in Human Somatic and Gene Therapy (1991) [GSTA.TXT; GSTA.W51]



APPENDIX D

Additional Resources on the Internet

BioData
http://www.biodata.com

BioMolecular Engineering Research Center
gopher://bmerc-gopher.bu.edu:70/1

BIO Online
http://www.bio.com

BioSpace
http://www.biospace.com

CBER FTP subdirectory
ftp://cdv2.cder.fda.gov/cber

CDER FTP site
ftp://cdv2.cder.fda.gov

Centers for Disease Control Web server
http://www.cdc.gov/

Center for Food Safety and Nutrition
http://vm.cfsan.fda.gov

FDA BBS
telnet://fdabbs.fda.gov; login:bbs

FDA Web site
http://www.fda.gov/fdahomepage.html

Federal Register and U.S. Code through GPO
telnet://librot1.lib.unc.edu; login: LIBRARY

Federal Register
http://gopher.nara.gov:70/1/register

Government Printing Office
http://www.access.gpo.gov/

HUM-MOLGEN - Communication Forum in Human Molecular Genetics
http://www.informatik.uni-rostock.de/HUM-MOLGEN/hum-mol.html

Human Genome Resources
gopher://marvel.loc.gov:70/11/global/med/med/genome

Immunology Home Page
http://golgi.harvard.edu/biopages/immuno.html

Intellectual Property Policies
http://infonet.welch.jhu.edu/policy/intellectual_prop_guide/som_intpol.html

Library of Congress gopher server
gopher://marvel.loc.gov/

Library of Congress Web server
http://lcweb.loc.gov/

National Center for Toxicological Research (NCTR)
http://www.fda.gov/nctr

Nest Group Molecular Biology WWW Resources
http://world.std.com/~nestgrp/molbiol.html

Patent and Trademark Office Web site
http://www.uspto.gov/

Patent Guidance Information
http://sunsite.unc.edu/patents/intropat.html

PharmWeb
http://www.mcc.ac.uk/pharmweb/

RAinfo - The Regulatory Affairs Information Home Page
http://www.nando.net/ads/ckbus/RAinfo/reglink1.htm

The National Center for Biotechnology Information
http://www.ncbi.nlm.nih.gov/

The World Wide Web Virtual Libary: Biotechnology
http://www.cato.com/interweb/cato/biotech/

US EPA Rules, Regulations and Legislation
http://www.epa.gov/Rules.html

U.S. Patent Office Archives
http://town.hall.org/cgi-bin/srch-patent