Matters To Be Discussed

Agenda items will include options for relationships between the tribes and ATSDR and CDC regarding the study of health effects from past, current, or future releases of radioactive and hazardous materials into the environment at Hanford, and proposed actions based on the findings of ATSDR and CDC health research and public health activities.

Agenda items are subject to change as priorities dictate.

Contact Person for More Information

Linda A. Carnes, Health Council Advisor, ATSDR, E–28, 1600 Clifton Road, NE., Atlanta, Georgia 30333, telephone 404/639–0730, FAX 404/639–0759.

Dated: June 30, 1995.

Carolyn J. Russell,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention (CDC).

[FR Doc. 95–16890 Filed 7–10–95; 8:45 am]

BILLING CODE 4163–70–M

Citizens Advisory Committee on Public Health Service Activities and Research at Department of Energy (DOE) Sites: Hanford Health Effects Subcommittee

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control and Prevention (CDC) announce the following meeting.

Name: Citizens Advisory Committee on Public Health Service Activities and Research at DOE Sites: Hanford Health Effects Subcommittee.

Times and Dates: 8 a.m.–5:30 p.m., July 27, 1995; 7 p.m.–8 p.m., July 27, 1995; 8 a.m.–3:30 p.m., July 28, 1995.

Place: Red Lion Inn, 2525 North 20th, Pasco, Washington 99301, telephone (509) 547–0701, FAX (509) 547–4278.

Status: Open to the public, limited only by the space available. The meeting room accommodates approximately 150 people.

Background

A Memorandum of Understanding (MOU) was signed in October 1990 and renewed in November 1992 between ATSDR and DOE. The MOU delineates the responsibilities and procedures for ATSDR's public health activities at DOE sites required under sections 104, 107, and 120 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or ''Superfund''). These activities include health consultations and public health assessments at DOE sites listed on, or proposed for, the Superfund National Priorities List and at sites that are the subject of petitions from the public; and other health-related activities such as epidemiologic studies, health surveillance, exposure and disease registries, health education, substance-specific applied research, emergency response, and preparation of toxicological profiles.

In addition, under an MOU signed in December 1990 with DOE, the Department of Health and Human Services (HHS) has been given the responsibility and resources for conducting analytic epidemiologic investigations of residents of communities in the vicinity of DOE facilities, workers at DOE facilities, and other persons potentially exposed to radiation or to potential hazards from non-nuclear energy production and use. HHS delegated program responsibility to CDC.

Purpose

The purpose of this meeting is to receive updates on issues related to the Technical Steering Panel and declassification of DOE documents; discuss issues and develop approaches to Public Outreach activities with ATSDR support; develop approaches to ATSDR and CDC health studies and medical monitoring programs, and receive updates on the Hanford Thyroid Disease Project and Lowell Sever's studies.

Matters to be Discussed

Agenda items include ATSDR's medical monitoring options, ATSDR's planning for a medical assistance program, current ATSDR health assessment activities. The subcommittee will solicit concerns which they will ask ATSDR and CDC to address.

Agenda items are subject to change as priorities dictate.

Contact Person for More Information

Linda A. Carnes, Health Council Advisor, ATSDR, E–28, 1600 Clifton Road, NE, Atlanta, Georgia 30333, telephone (404) 639–0730, FAX (404) 639–0759.

Dated: June 30, 1995.

Carolyn J. Russell,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention (CDC).

[FR Doc. 95–16889 Filed 7–10–95; 8:45 am]

BILLING CODE 4163–70–M

Food and Drug Administration

[Docket No. 95D–0164]

FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance document concerning the use of pilot facilities for the development and manufacture of biological products. The guidance document, entitled ''Center for Biologics Evaluation and Research; Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Guidance,'' provides guidance by the Center for Biologics Evaluation and Research (CBER) to manufacturers of biological products to clarify the licensing requirements for the use of small scale and pilot facilities for the development and manufacture of biological products. These facilities are sometimes collectively referred to by industry as pilot facilities. This guidance document is intended to provide increased flexibility for industry without diminishing public health protection.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Comments should be identified with the docket number found in brackets in the heading of the document. Two copies of all comments are to be submitted, except that individuals may submit one copy. The comments received are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Jean M. Olson, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 400 South, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION: CBER recognizes that development of important new biological products is expensive and time consuming, and that companies must be able to forecast and evaluate their expenditures for this process. Constructing a new facility to manufacture a product that has not been fully tested in clinical trials could result in a company being unable to recover a major capital expenditure if the product is not ultimately brought to market. CBER also recognizes that for some companies the best financial option may be the use of a pilot facility where a product may be manufactured at a smaller scale than would be ultimately desired for an approved product.

While CBER does not object to the use of pilot production facilities for the manufacture of clinical material, many companies are concerned that these facilities would not be eligible for establishment licensure. This guidance document is intended to clearly articulate that pilot facilities are eligible for licensure. The guiding principle is that an application for establishment licensure can be made for any facility

(regardless of the scale of manufacture) which is fully qualified, validated, operates in accordance with current good manufacturing practices (CGMP's), and otherwise complies with applicable law and regulations. In order to further streamline the approval process, the agency is currently considering changing its procedures to eliminate the requirement for a separate establishment license for certain well defined classes of biologic products. Because of recent scientific advances, both in methods of manufacture and in methods of analysis, some products developed through biotechnology can be characterized in ways not historically considered possible. Thus, the agency is considering allowing ''biotech'' products that are well characterized to be regulated under a single application. The agency plans to hold a scientific conference in the fall of 1995, to develop a definition of well characterized products that may be amenable to regulation under new procedures.

This guidance document describes the conditions and procedures for submitting establishment license applications (ELA's) for pilot facilities and for subsequent transfer of product manufacturing to a different facility. The guidance document provides information concerning: (1) Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility; (2) submissions for approval to use a pilot facility for manufacture of a product; (3) submissions for approval to use a different manufacturing facility while a product license application (PLA) for a product manufactured in a pilot facility and an ELA for a pilot facility are pending; (4) submissions for approval to use a different manufacturing facility when a product and pilot facility are currently licensed; and (5) submission of a PLA based on data obtained from a product made in a pilot facility when licensure of the product manufactured in the pilot facility and of the pilot facility is not sought.

The guidance also addresses review timeframes and submission times, product consistency, data comparing products made in different facilities, and product availability at the time of product licensure.

In addition, FDA intends to revise the policy statement entitled ''Manufacturing Arrangements for Licensed Biologics'' published in the **Federal Register** of November 25, 1992 (57 FR 55544) to accommodate these procedures.

This guidance document is not binding on either FDA or manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The title and text of the guidance document follows:

Center for Biologics Evaluation and Research; Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Guidance

I. Introduction

Biological products, which generally include vaccines, blood and blood products, allergenic extracts, and biological therapeutics, are regulated under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), as well as the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). The PHS Act requires that biological products be propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license. Lack of clarity about licensing requirements has led some applicants to make major investments in large scale manufacturing facilities before initiating the clinical trial(s) necessary to demonstrate the safety and effectiveness of their products. Such investments can result in significant financial loss if the product is not ultimately brought to market. In this document, the Center for Biologics Evaluation and Research (CBER) is providing guidance to manufacturers and developers of biological products to clarify licensing procedures for the use of pilot facilities for the manufacture of biological products. CBER considers a pilot production to be a procedure and facility fully representative of and simulating that to be applied on a full commercial scale. For example, the methods of cell expansion, harvest, and product purification should be identical except for scale of production. These facilities are sometimes collectively referred to by industry as ''pilot facilities'' and will be referred to as ''pilot'' in this document. These facilities are to be distinguished from facilities used in research and development that may not operate under appropriate current good manufacturing practices (CGMP's).

II. Background

CBER recognizes that development of important new biological products may be expensive and time consuming and that companies must be able to forecast and evaluate their expenditures for this process. Constructing a large scale facility to manufacture a product that has not been fully tested in clinical trials could result in a major capital loss if delays occur or the product is not ultimately brought to market. CBER also recognizes that for some companies, the best financial option may be the use of a pilot facility where a product may be manufactured at a smaller scale than might be eventually desired for an approved product. While CBER has not objected to the use of pilot facilities for the manufacture of clinical material (provided such manufacture is in compliance with requirements applicable to investigational drugs), many companies are concerned that these facilities and the product manufactured in them would not be eligible for licensure. An application for establishment licensure can be made for any facility (regardless of the scale of manufacture) that has been fully qualified and validated, that operates under CGMP's, and that otherwise complies with applicable laws and regulations. This guidance document describes the conditions and procedures for submitting such application(s) and for subsequent, optional transfer of product manufacturing to a different manufacturing facility.

III. Guidance

The following provides information on the submission of product license applications (PLA's) and establishment license applications (ELA's) and investigational new drug applications (IND's) for products manufactured in a pilot facility.

1. Use of a product manufactured in a pilot facility in clinical trials conducted to demonstrate safety and effectiveness and optional transition to a different facility.

IND's for all products should include information that describes where the material for the clinical trial(s) used to demonstrate safety and effectiveness is or was manufactured. Data submitted in support of licensure of a biological product can be obtained using a product manufactured in a pilot facility. In the event that a product manufactured in new facilities and/or scaled-up processes or facilities is intended to be used at a later date for either completion of the clinical trial(s) demonstrating safety or effectiveness or for licensable product, the time tables, new locations, and processes should be identified in the IND. A protocol for comparing products should also be submitted. Data which compares a product made in a new facility or with new processes to a product used in earlier clinical studies should be submitted to the IND before including the new product in the clinical trial(s). If the product made in the new facility or by the new process will not be used in the clinical trials used to demonstrate safety or effectiveness, the data comparing the two products should be submitted in the IND, PLA, or PLA supplement. A description of any manufacturing changes that were made as a result of using a new facility or new processes and stability data should also be submitted to the IND or PLA as appropriate.

2. Submissions for approval to use a pilot facility for manufacture of a product.

Information and data submitted in the PLA should be obtained using a product manufactured in the pilot facility. The ELA should include a completed Form FDA 3210; Application for Establishment License for Manufacture of Biological Products (FDA

Form 3210), which describes the pilot facility. If the facility is already licensed, an ELA supplement that contains information specific to the new product should be submitted. The facility and equipment, regardless of scale, should have undergone appropriate qualification and validation and should be in compliance with applicable regulations, including, but not limited to, 21 CFR parts 210, 211, 600 and 820. A pre-license inspection will be conducted prior to the approval of the PLA and ELA or ELA supplement. The PLA and ELA may be submitted at different times, provided a statement is included in any PLA or ELA submission confirming that the facility is ready for inspection and indicating the approximate date for the companion application submission. CBER intends to review PLA's and ELA's submitted at different times under the normal timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard applications, 6 months for priority applications, and 6 months for supplements). Because CBER issues the ELA and PLA concurrently, timing of submission of the companion applications should be carefully considered. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

3. Submissions for approval to use a different manufacturing facility while a PLA for a product manufactured in a pilot facility and an ELA for a pilot facility are pending.

In this case, a PLA for a product made in a pilot facility and ELA for the pilot facility are under review as outlined in section III. 2 of this guidance. FDA's inspection of the pilot facility may or may not have occurred. The applicant is now requesting licensure of a different facility in addition to, or in lieu of, licensure of the pilot facility. The following information should be submitted to the pending PLA: a description of manufacturing changes which have occurred, data comparing products made in the new and old facilities, and documentation of process validation and stability data for a product manufactured in the new facility. CBER intends to consider the submission to be a separate PLA filing that will be assigned a new reference number and a 6-month review timeframe. A new ELA that contains a completed ELA Form 3210 describing the new facility should also be submitted. If the new facility is already licensed, the applicant should submit a supplement to the approved ELA with the information specific to the new product. A statement confirming that the new facility is ready for inspection should be included in the new PLA filing and the ELA or ELA supplement at the time of submission. Concurrent review of the pilot facility will continue unless the applicant is no longer requesting approval to market lots manufactured in the pilot facility. If the applicant does not wish to pursue licensure of lots made in a pilot facility, a request may be made in writing that the pending ELA for the pilot facility be withdrawn; however, FDA may still conduct an inspection. In this case, lots manufactured in the pilot facility could be used in other clinical trials but could not be marketed. CBER intends to review the ELA for the new facility within new application timeframes under the managed review process. As such, CBER intends to issue a new reference number and review priority applications within 6 months, standard applications within 12 months, and supplements within 6 months. CBER intends to review the new PLA filing within 6 months. An inspection of both facilities will be performed if the applicant requests licensure of both. Applicants should specify which establishment is a higher priority for licensure and CBER may choose to concentrate its resources on reviewing the application for that facility first. Either combination of product and establishment may be licensed when all information has been reviewed and found to be acceptable. The pilot facility and product may be eligible for licensure before the new facility and product are ready for approval. In regard to the timing of submissions, it should be noted that CBER's timeframe for review of a new ELA may be longer (12 months for standard application and 6 months for priority application under the managed review process) than that for review of the new PLA filing. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

4. Submissions for approval to use a different manufacturing facility when a product and pilot facility are currently licensed.

A supplement to the approved PLA for a product made in a pilot facility and an ELA or ELA supplement for the new facility should be submitted when the applicant wishes to obtain licensure for a different facility and product manufactured in it. The PLA supplement should contain information on a product manufactured in the new facility, including a description of manufacturing changes that have occurred. (See ''Changes to be Reported for Product and Establishment License Applications; Guidance'' (60 FR 17535, April 6, 1995)). Data comparing products made in each facility, and process validation and stability data for a product manufactured in the new facility should also be provided. If a new ELA is submitted, it should contain a completed ELA Form 3210 that describes the new facility. If the proposed facility is already a licensed facility, an ELA supplement should be submitted that contains information specific to the new product. A statement confirming that the facility is ready for inspection should be included with each submission. CBER intends to review PLA's, ELA's, and supplements according to the timeframe targets of the managed review process (6 months for manufacturing and facility changes) and intends to approve ELA's and PLA's or supplements concurrently, when all information has been reviewed and found acceptable. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

5. Submission of a PLA based on data obtained from a product made in a pilot facility when licensure of the product manufactured in the pilot facility and pilot facility is not sought.

CBER will allow submission of a PLA based on data obtained from clinical trials using a product made in a pilot facility when the pilot facility is not intended to be licensed. In order to verify data comparing a product made in a pilot facility and used in the clinical trials to a product made in the facility to be licensed, the pilot facility should be available for inspection up to the time the applicant obtains licensure of the product in the new facility. A product used in clinical trials to support licensure can be made in a facility for which the applicant does not intend to seek licensure, but only a licensed product made in a licensed facility may be marketed. The PLA should contain information and data on a product manufactured in the pilot facility and a statement that the pilot facility is ready for inspection at the time of submission. An inspection of the pilot facility may be performed in some cases. Stability data from a product made in the pilot facility, if representative of a product manufactured in the facility intended to be licensed, can be used in support of a proposed dating period. A separate, original ELA for the facility intended for licensure may be submitted concurrently with the PLA or after review of the PLA has begun. The ELA for the facility intended for licensure should be submitted when a product in support of approval has been manufactured, a product is available for review, and the facility is ready for inspection. If submission of the ELA occurs after PLA review has begun, an accompanying PLA supplement containing data comparing products made in both facilities should include stability data, process validation, and a description of any manufacturing changes (see Guidance (60 FR 17535)). CBER intends to review each ELA and PLA under the current timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard and 6 months for priority applications; 6 months for manufacturing supplements). While an ELA and PLA need not be submitted concurrently, applicants are reminded that CBER intends to approve ELA's and PLA's concurrently. CBER intends to consider failure to submit a companion application within 6 months of receipt of a standard application or 3 months of receipt of a priority application to be grounds for issuing a not approvable letter to the applicant.

6. Demonstration of product consistency and data comparing products made in different facilities.

When manufacture of a product is transferred from a pilot facility to a different facility, a demonstration of product consistency, data comparing the two products, and process validation should be submitted in the PLA supplement or amendment to the IND. Retention samples from the pilot facility should be stored under

controlled conditions in sufficient quantity to conduct the side-by-side testing of products. Applicants are encouraged to discuss with CBER what data are necessary to compare products, as such data may range from analytical testing to full clinical trial(s).

7. Review timeframes and submission times

There may be cases where applicants wish to submit an ELA for a pilot facility prior to submitting a companion PLA. A statement that the facility is ready for inspection at the time of submission should be included. FDA ordinarily intends to inspect at the time the facility is manufacturing the product for which licensure is sought. It is possible that, in some cases, inspection of the establishment could take place before the submission of the PLA. It is also possible for the ELA to be submitted after the PLA as discussed above.

CBER intends to review PLA's and ELA's submitted at different times under the normal timeframe targets of the managed review process (from the date of receipt at CBER, 12 months for standard and 6 months for priority applications; 6 months for supplements). CBER intends to issue the appropriate action letter (approved, approvable, or not approvable) to complete its action on any application.

Applicants should be aware that submitting the ELA and PLA at separate times will not necessarily reduce the approval time when compared to concurrent submission. Early submission of applications may, however, allow earlier feedback from CBER on deficiencies in an application that can be addressed by the applicant sooner than would otherwise be possible. In all cases described above, CBER intends to approve PLA's, ELA's, or supplements concurrently.

In cases of shared manufacturing arrangements (see 57 FR 55544 at 55545), the PLA's for the intermediate product(s) and end product should be submitted concurrently in order for a complete review of the product to occur, since determining the approvability of the end product will depend upon information in the intermediate product PLA's. The ELA's may be submitted at different times from the PLA's.

Applicants should consider carefully the consequences of the timing of any submission on the use of CBER resources. It is expected that applicants will use the flexible submission times in cases of need. Applicants should recognize that the filing of submissions which are premature or incomplete will result in unnecessary resource commitments by CBER and the applicant. It is therefore recommended that applicants do not submit an ELA before favorable preliminary data or information from clinical trials of the product is available. For products intended for use in serious and life-threatening diseases, applicants should consider submitting the ELA and PLA concurrently to prevent a situation from occurring where otherwise approvable product cannot be approved because the facility is not yet ready to be licensed.

If a scenario exists that is not covered in this guidance document, the applicant should seek guidance by contacting the appropriate applications division in the Offices of Therapeutics Research and Review, Blood Research and Review, or Vaccines Research and Review, or the Division of Establishment Licensing.

8. Availability of product at the time of licensure

If an applicant requests licensure for a pilot facility, this choice may affect the amount of product available at the time of approval. For important new products for use in treating serious and life-threatening illnesses, the ramifications of limited availability of the product at the time of approval should be assessed by the applicant.

Dated: June 26, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–17022 Filed 7–7–95; 10:53 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE INTERIOR

National Biological Service

Information Collection Submitted to the Office of Management and Budget for Review Under the Paperwork Reduction Act

The proposal for the collection of information listed below has been submitted to the Office of Management and Budget for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). An expedited review has been requested in accordance with the Act so that approval can be received by August 18, 1995, permitting the National Biological Service to comply with Executive Order 12862 reporting requirements for 1995. Copies of the proposed collection of information and related forms may be obtained by contacting the Service's clearance officer at the phone number listed below. Comments and suggestions on the proposal should be made directly to the bureau clearance officer and the Office of Management and Budget, Paperwork Reduction Project, Washington, DC 20503, telephone (202) 395–7340.

Title: Generic Clearance for Measurement of Client Satisfaction with National Biological Service Products and Services

Abstract: The National Biological Service (NBS) is initiating a process with standard form to gather information about its customers' level of satisfaction with its products and services. When certain NBS products and services are delivered to a client, the client will also be given a Client Response sheet on which the client is invited to rate his/her satisfaction with the product or service and offer any additional comments he/she wishes to make. The information from the responses will be summarized annually and the results used to improve NBS products and services. Copies of the final report of the summarized information will be provided to NBS' clients. This process and report will allow NBS to comply with Executive Order 12862 and the Government Performance and Results Act (44 U.S.C. Chapter 35)

Bureau Form Number: None

Frequency: Annually

Description of Respondents: Federal government officials and secondarily state and local government officials engaged in policy making, regulation, or management of public trust lands and resources

Estimated Completion time per Respondent: 0.17 Hour

Individuals invited to Respond annually: 2000

Estimate annual Responses: 300

Annual Burden Hours: 50

Bureau Clearance Officer: Don Minnich, (202) 482–4838

Dated: June 23, 1995.

F. Eugene Hester,

Deputy Director.

[FR Doc. 95–16901 Filed 7–10–95; 8:45 am]

BILLING CODE 4310–DP–M

INTERSTATE COMMERCE COMMISSION

[Finance Docket No. 32681]

H. Peter Claussen and Linda C. Claussen—Continuance in Control Exemption—Georgia & Florida Railroad Co., Inc.

AGENCY: Interstate Commerce Commission.

ACTION: Notice of exemption.

SUMMARY: The Commission under 49 U.S.C. 10505 exempts from the prior approval requirements of 49 U.S.C. 11343, et seq., the continuance in control by H. Peter Claussen and Linda C. Claussen (the Claussens) of the Georgia & Florida Railroad Co., Inc. (G&F), upon G&F becoming a rail carrier, subject to standard labor protective conditions. The Claussens presently control Albany Bridge Company, Inc.; Gulf and Ohio Railways, Inc., which operates the Mississippi Delta Railroad and the Atlantic & Gulf Railroad; Wiregrass Central Railroad Company, Inc.; H&S Railroad Company, Inc.; Piedmont & Atlantic Railroad Co., Inc.; and Rocky Mount & Western Railroad Co., Inc. G&F filed a notice of exemption in Finance Docket No. 32680 to exempt its acquisition, lease, and