Reason: Surrendered license voluntarily.

T. A. Zook,

Deputy Director, Bureau of Tariffs, Certification and Licensing.

[FR Doc. 99–21439 Filed 8–17–99; 8:45 am]

BILLING CODE 6730–01–M

FEDERAL MARITIME COMMISSION

[Docket No. 99–15]

Notice of Investigation

Notice is given that the Commission, on August 13, 1999, served an Order of Investigation and Hearing on respondents David P. Kelly and West Indies Shipping and Trading, Inc. The Order institutes a formal investigation to determine whether respondents violated sections 8(a)(1), 10(a)(1), 19(a) and 19(b)(1) of the Shipping Act of 1984, 46 U.S.C. app. §§ 1707(a)(1), 1709(a)(1), 1718(a) and 1718(b)(1), by operating as a non-vessel-operating common carrier without a tariff on file with the Commission prior to May 1, 1999, and thereafter without a license, a publicly available tariff, a bond or other form of surety; and by providing inaccurate descriptions of cargo to ocean common carriers in order to obtain lower rates. Moreover, should violations be found, the proceeding will determine whether to impose civil penalties and, if so, in what amount, and whether to issue an appropriate cease and desist order. The full text of the Order may be viewed on the Commission's home page at www.fmc.gov, or at the Office of the Secretary, Room 1046, 800 N. Capitol Street, NW, Washington, DC. Any person may file a petition for leave to intervene in accordance with 46 CFR 502.72.

Ronald D. Murphy,

Assistant Secretary.

[FR Doc. 99–21440 Filed 8–17–99; 8:45 am]

BILLING CODE 6730–01–M

FEDERAL RESERVE SYSTEM

Formations of, Acquisitions by, and Mergers of Bank Holding Companies

The companies listed in this notice have applied to the Board for approval, pursuant to the Bank Holding Company Act of 1956 (12 U.S.C. 1841 *et seq.*) (BHC Act), Regulation Y (12 CFR Part 225), and all other applicable statutes and regulations to become a bank holding company and/or to acquire the assets or the ownership of, control of, or the power to vote shares of a bank or bank holding company and all of the banks and nonbanking companies owned by the bank holding company, including the companies listed below.

The applications listed below, as well as other related filings required by the Board, are available for immediate inspection at the Federal Reserve Bank indicated. The application also will be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing on the standards enumerated in the BHC Act (12 U.S.C. 1842(c)). If the proposal also involves the acquisition of a nonbanking company, the review also includes whether the acquisition of the nonbanking company complies with the standards in section 4 of the BHC Act (12 U.S.C. 1843). Unless otherwise noted, nonbanking activities will be conducted throughout the United States.

Unless otherwise noted, comments regarding each of these applications must be received at the Reserve Bank indicated or the offices of the Board of Governors not later than September 13, 1999.

A. Federal Reserve Bank of Atlanta (Lois Berthaume, Vice President) 104 Marietta Street, N.W., Atlanta, Georgia 30303-2713:

1. Community National Bancorporation, Ashburn, Georgia; to acquire 100 percent of the voting shares of Cumberland National Bank, St. Marys, Georgia, (in organization).

2. Equitex, Inc., Englewood, Colorado; to become a bank holding company by acquiring 100 percent of the voting shares of First TeleBanc Corporation, Boca Raton, Florida, and thereby indirectly acquire Net First National Bank, Boca Raton, Florida.

3. Florida Business Bancgroup, Inc., Tampa, Florida; to become a bank holding company by acquiring 100 percent of the voting shares of Bay Cities Bank, Tampa, Florida, (in organization).

Board of Governors of the Federal Reserve System, August 13, 1999.

Jennifer J. Johnson,

Secretary of the Board.

[FR Doc. 99–21432 Filed 8–17–99; 8:45 am]

BILLING CODE 6210–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D–0374]

International Conference on Harmonisation; Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled ''Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.'' The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance provides guidance on general principles for the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. The guidance is intended to assist in the establishment of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

DATES: Effective August 18, 1999. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Copies of the guidance are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573. Single copies of the guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852, or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Neil D. Goldman, Center for Biologics Evaluation and Research (HFM–20), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0377.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of June 9, 1998 (63 FR 31506), FDA published a draft tripartite guidance entitled ''Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.'' The notice gave interested persons an opportunity to submit comments by July 24, 1998.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies on March 11, 1999.

In accordance with FDA's good guidance practices (62 FR 8961, February 27, 1997), this document has been designated a guidance, rather than a guideline.

The guidance provides guidance on general principles for the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. The guidance is intended to assist in the establishment of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

This guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

As with all of FDA's guidances, the public is encouraged to submit written comments with new data or other new information pertinent to this guidance. The comments in the docket will be periodically reviewed, and, where appropriate, the guidance will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guidance to the Dockets Management Branch (address above). 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. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet at ''http://www.fda.gov/cder/guidance/index.htm'' or at CBER's World Wide Web site at ''http://www.fda.gov/cber/publications.htm''.

The text of the guidance follows:

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products[1]

Table of Contents

1.0 Introduction

1.1 Objective

This guidance document provides guidance on general principles for the setting and justification, to the extent possible, of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

1.2 Background

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of

[1]This guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. ''Conformance to specification'' means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which many of the specifications are based, adherence to good manufacturing practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

1.3 Scope

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types, such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, deoxyribonucleic acid (DNA) products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components. A separate ICH draft guidance, ''Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances'' addresses specifications and other criteria for chemical substances.

This document does not recommend specific test procedures or specific acceptance criteria, nor does it apply to the regulation of preclinical and/or clinical research material.

2.0 Principles for Consideration in Setting Specifications

2.1 Characterization

Characterization of a biotechnological or biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) by appropriate techniques is necessary to allow relevant specifications to be established. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, data from stability studies, and relevant development data.

Extensive characterization is performed in the development phase and, where necessary, following significant process changes. At the time of submission, the product should have been compared with an appropriate reference standard, if available. When feasible and relevant, it should be compared with its natural counterpart. Also, at the time of submission, the manufacturer should have established appropriately characterized in-house reference materials which will serve for biological and physicochemical testing of production lots. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

2.1.1 Physicochemical properties

A physicochemical characterization program will generally include a determination of the composition, physical properties, and primary structure of the desired product. In some cases, information regarding higher-order structure of the desired product (the fidelity of which is generally inferred by its biological activity) may be obtained by appropriate physicochemical methodologies.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated post-translationally modified forms (e.g., glycoforms). These forms may be active and their presence may have no deleterious effect on the safety and efficacy of the product (section 2.1.4). The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity, efficacy, and safety (including immunogenicity) of individual forms may not be necessary.

Heterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product. Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterized to ensure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they are considered product-related substances. When process changes and degradation products result in heterogeneity patterns that differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated.

Analytical methods to elucidate physicochemical properties are listed in appendix 6.1. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

2.1.2 Biological activity

Assessment of the biological properties constitutes an equally essential step in establishing a complete characterization profile. An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect.

A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include:

- Animal-based biological assays, which measure an organism's biological response to the product;
- Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level; and
- Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.

Other procedures, such as ligand and receptor binding assays, may be acceptable.

Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product that is linked to the relevant biological properties, whereas quantity (expressed in mass) is a physicochemical measure of protein content. Mimicking the biological activity in the clinical situation is not always necessary. A correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies.

The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized. Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.

Often, for complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure. Importantly, a biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where:

- Sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
- There exists a well-established manufacturing history.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

For the purpose of lot release (section 4), the choice of relevant quantitative assay (biological and/or physicochemical) should be justified by the manufacturer.

2.1.3 Immunochemical properties

When an antibody is the desired product, its immunological properties should be fully characterized. Binding assays of the antibody to purified antigens and defined regions of antigens should be performed, as feasible, to determine affinity, avidity and immunoreactivity (including cross-reactivity). In addition, the target molecule bearing the relevant epitope should be biochemically defined and the epitope itself defined, when feasible.

For some drug substances or drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., enzyme linked immunosorbent assay (ELISA), Western-blot) utilizing antibodies that recognize different epitopes of the protein molecule. Immunochemical properties of a protein may serve to establish its identity, homogeneity, or purity, or serve to quantify it.

If immunochemical properties constitute lot release criteria, all relevant information pertaining to the antibody should be made available.

2.1.4 Purity, impurities, and contaminants

- *Purity*

The determination of absolute, as well as relative, purity presents considerable analytical challenges, and the results are highly method dependent. Historically, the relative purity of a biological product has been expressed in terms of specific activity (units of biological activity per milligram of product), which is also highly method dependent. Consequently, the purity of the drug substance and drug product is assessed by a combination of analytical procedures.

Due to the unique biosynthetic production process and molecular characteristics of biotechnological and biological products, the drug substance can include several molecular entities or variants. When these molecular entities are derived from anticipated post-translational modification, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and/or storage and have properties comparable to the desired product, they are considered product-related substances and not impurities (section 2.1.1).

Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.

For the purpose of lot release (section 4), an appropriate subset of methods should be selected and justified for determination of purity.

- *Impurities*

In addition to evaluating the purity of the drug substance and drug product, which may be composed of the desired product and multiple product-related substances, the manufacturer should also assess impurities which may be present. Impurities may be either process- or product-related. They can be of known structure, partially characterized, or unidentified. When adequate quantities of impurities can be generated, these materials should be characterized to the extent possible and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, i.e., cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (see appendix, section 6.2.1). Product-related impurities (e.g., precursors, certain degradation products) are molecular variants arising during manufacture and/or storage that do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Further, the acceptance criteria for impurities should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.

Individual and/or collective acceptance criteria for impurities (product-related and process-related) should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary (section 2.3).

Examples of analytical procedures that may be employed to test for the presence of impurities are listed in appendix 6.2. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

- *Contaminants*

Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases) and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product specifications (section 2.3). For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in ICH guidances ''Q5A Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin'' and ''Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products'' should be considered.

2.1.5 Quantity

Quantity, usually measured as protein content, is critical for a biotechnological and biological product and should be determined using an appropriate assay, usually physicochemical in nature. In some cases, it may be demonstrated that the quantity values obtained may be directly related to those found using the biological assay. When this correlation exists, it may be appropriate to use measurement of quantity rather than the measurement of biological activity in manufacturing processes, such as filling.

2.2 Analytical Considerations

2.2.1 Reference standards and reference materials

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities, and process-related impurities may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability should also be provided.

2.2.2 Validation of analytical procedures

At the time the application is submitted to the regulatory authorities, applicants should have validated the analytical procedures used in the specifications in accordance with the ICH guidances ''Q2A Validation of Analytical Procedures: Definitions and Terminology'' and ''Q2B Validation of Analytical Procedures: Methodology,'' except where there are specific issues for unique tests used for analyzing biotechnological and biological products.

2.3 Process Controls

2.3.1 Process-related considerations

Adequate design of a process and knowledge of its capability are part of the strategy used to develop a manufacturing process that is controlled and reproducible, yielding a drug substance or drug product that meets specifications. In this respect, limits are justified based on critical information gained from the entire process spanning the period from early development through commercial-scale production.

For certain impurities, testing of either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies. This testing can include verification at commercial scale in accordance with regional regulations. It is recognized that only limited data may be available at the time of submission of an application. This concept may, therefore, sometimes be implemented after marketing authorization, in accordance with regional regulations.

2.3.2 In-process acceptance criteria and action limits

In-process tests are performed at critical decision-making steps and at other steps where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The results of in-process testing may be recorded as action limits or reported as acceptance criteria. Performing such testing may

eliminate the need for testing of the drug substance or drug product (section 2.3.1). In-process testing for adventitious agents at the end of cell culture is an example of testing for which acceptance criteria should be established.

The use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer, may be used to initiate investigation or further action. They should be further refined as additional manufacturing experience and data are obtained after product approval.

2.3.3 Raw materials and excipient specifications

The quality of the raw materials used in the production of the drug substance (or drug product) should meet standards appropriate for their intended use. Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures that make use of affinity chromatography (for example, employing monoclonal antibodies) should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product. Appropriate information pertaining to the antibody should be made available.

The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.

2.4 Pharmacopoeial Specifications

Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria which, where relevant, are part of the evaluation of either the drug substance or drug product. Such monographs, applicable to biotechnological and biological products, generally include, but are not limited to, tests for sterility, endotoxins, microbial limits, volume in container, uniformity of dosage units, and particulate matter. With respect to the use of pharmacopoeial methods and acceptance criteria, the value of this guidance is linked to the extent of harmonization of the analytical procedures of the pharmacopoeias. The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

2.5 Release Limits Versus Shelf-Life Limits

The concept of release limits versus shelf-life limits may be applied where justified. This concept pertains to the establishment of limits which are tighter for the release than for the shelf-life of the drug substance or drug product. Examples where this may be applicable include potency and degradation products. In some regions, the concept of release limits may only be applicable to in-house limits and not to the regulatory shelf-life limits.

2.6 Statistical Concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

3.0 Justification of the Specification

The setting of specifications for drug substance and drug product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation or validation, adherence to good manufacturing practices, stability testing, and testing for consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

- Specifications are linked to a manufacturing process.

Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities, and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns which differ from those observed in the material used during preclinical and clinical development. The significance of these alterations should be evaluated.

- Specifications should account for the stability of drug substance and drug product.

Degradation of drug substance and drug product, which may occur during storage, should be considered when establishing specifications. Due to the inherent complexity of these products, there is no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of which tests should be included will be product specific. The manufacturer is referred to the ICH guidance ''Q5C Stability Testing of Biotechnological/Biological Products.''

- Specifications are linked to preclinical and clinical studies.

Specifications should be based on data obtained for lots used in preclinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.

- Specifications are linked to analytical procedures.

Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities. Such attributes can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, it is not unusual for the analytical technology to evolve in parallel with the product. Therefore, it is important to confirm that data generated during development correlate with those generated at the time the marketing application is filed.

4.0 Specifications

Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, data from stability studies, and relevant development data.

In some cases, testing at production stages rather than testing at the finished drug substance or drug product stages may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and included in the specification of drug substance or drug product in accordance with the requirements of the regional regulatory authorities.

4.1 Drug Substance Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug substances (for analytical procedures, see section 2.2.2). Pharmacopoeial tests (e.g., endotoxin detection) should be performed on the drug substance, where appropriate. Additional drug substance specific acceptance criteria may also be necessary.

4.1.1 Appearance and description

A qualitative statement describing the physical state (e.g., solid, liquid) and color of a drug substance should be provided.

4.1.2 Identity

The identity test(s) should be highly specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity. The identity test(s) can be qualitative in nature. Some of the methods typically used for characterization of the product as described in section 2.1 and in appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

4.1.3 Purity and impurities

The absolute purity of biotechnological and biological products is difficult to determine and the results are method dependent (section 2.1.4). Consequently, the purity of the drug substance is usually estimated by a combination of methods. The

choice and optimization of analytical procedures should focus on the separation of the desired product from product-related substances and from impurities.

The impurities observed in these products are classified as process-related and product-related:

- Process-related impurities (section 2.1.4) in the drug substance may include cell culture media, host cell proteins, DNA, monoclonal antibodies or chromatographic media used in purification, solvents, and buffer components. These impurities should be minimized by the use of appropriate, well-controlled manufacturing processes.
- Product-related impurities (section 2.1.4) in the drug substance are molecular variants with properties different from those of the desired product formed during manufacture and/or storage.

For the impurities, the choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities. Individual and/or collective acceptance criteria for impurities should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary (section 2.3).

4.1.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological or biological drug substance and/or drug product. When an appropriate potency assay is used for the drug product (section 4.2.4), an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage. In some cases, the measurement of specific activity may provide additional useful information.

4.1.5 Quantity

The quantity of the drug substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be independent of a reference standard or material. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

4.2 Drug Product Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug products. Each section (4.2.1–4.2.5) is cross-referenced to respective sections (4.1.1–4.1.5) under Drug Substance Specification. Pharmacopoeial requirements apply to the relevant dosage forms. Typical tests found in the pharmacopoeia include, but are not limited to, sterility, endotoxin, microbial limits, volume in container, particulate matter, uniformity of dosage units, and moisture content for lyophilized drug products. If appropriate, testing for uniformity of dosage units may be performed as in-process controls, and corresponding acceptance criteria are set.

4.2.1 Appearance and description

A qualitative statement describing the physical state (e.g., solid, liquid), color, and clarity of the drug product should be provided.

4.2.2 Identity

The identity test(s) should be highly specific for the drug product and should be based on unique aspects of its molecular structure and other specific properties. The identity test(s) can be qualitative in nature. While it is recognized that in most cases a single test is adequate, more than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity for some products. Some of the methods typically used for characterization of the product as described in section 2.1 and in appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

4.2.3 Purity and impurities

Impurities may be generated or increased during manufacture and/or storage of the drug product. These may be either the same as those occurring in the drug substance itself, process-related, or degradation products which form specifically in the drug product during formulation or during storage. If impurities are qualitatively and quantitatively (i.e., relative amounts and/or concentrations) the same as in the drug substance, testing is not considered necessary. If impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established.

Acceptance criteria and analytical procedures should be developed and justified, based upon previous experience with the drug product, to measure changes in the drug substance during the manufacture and/or storage of the drug product.

The choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities including degradation products, and from excipients.

4.2.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological and biological drug substance and/or drug product. When an appropriate potency assay is used for the drug substance, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product. However, the rationale for such a choice should be provided.

4.2.5 Quantity

The quantity of the drug substance in the drug product, usually based on protein content (mass), should be determined using an appropriate assay. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

4.2.6 General tests

Physical description and the measurement of other quality attributes are often important for the evaluation of the drug product functions. Examples of such tests include pH and osmolarity.

4.2.7 Additional testing for unique dosage forms

It should be recognized that certain unique dosage forms may need additional tests other than those mentioned above.

5.0 Glossary

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of manufacture should meet.

Action limit: An internal (in-house) value used to assess the consistency of the process at less critical steps.

Biological activity: The specific ability or capacity of the product to achieve a defined biological effect. Potency is the quantitative measure of the biological activity.

Contaminants: Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product.

Degradation products: Molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

Desired Product: (1) The protein that has the expected structure, or (2) the protein that is expected from the DNA sequence and anticipated post-translational modification (including glycoforms), and from the intended downstream modification to produce an active biological molecule.

Drug product (Dosage form; Finished product): A pharmaceutical product type that contains a drug substance, generally in association with excipients.

Drug substance (Bulk material): The material that is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components, such as buffers.

Excipient: An ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

Impurity: Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient including buffer components. It may be either process- or product-related.

In-house primary reference material: An appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

In-house working reference material: A material prepared similarly to the primary

reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

Potency: The measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties.

Process-related impurities: Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).

Product-related impurities: Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Product-related substances: Molecular variants of the desired product formed during manufacture and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

Reference standards: International or national standards.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. ''Conformance to specification'' means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

6.0 Appendices

6.1 Appendix for Physiochemical Characterization

This appendix provides examples of technical approaches that might be considered for structural characterization and confirmation, and evaluation of physicochemical properties of the desired product, drug substance, and/or drug product. The specific technical approach employed will vary from product to product, and alternative approaches, other than those included in this appendix, will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed and should be utilized when appropriate.

6.1.1 Structural characterization and confirmation

(a) Amino acid sequence

The amino acid sequence of the desired product should be determined to the extent possible using approaches such as those described in items (b) through (e) and then compared with the sequence of the amino acids deduced from the gene sequence of the desired product.

(b) Amino acid composition

The overall amino acid composition is determined using various hydrolytic and analytical procedures and compared with the amino acid composition deduced from the gene sequence for the desired product, or the natural counterpart, if considered necessary. In many cases, amino acid composition analysis provides some useful structural information for peptides and small proteins, but such data are generally less definitive for large proteins. Quantitative amino acid analysis data can also be used to determine protein content in many cases.

(c) Terminal amino acid sequence

Terminal amino acid analysis is performed to identify the nature and homogeneity of the amino- and carboxy-terminal amino acids. If the desired product is found to be heterogeneous with respect to the terminal amino acids, the relative amounts of the variant forms should be determined using an appropriate analytical procedure. The sequence of these terminal amino acids should be compared with the terminal amino acid sequence deduced from the gene sequence of the desired product.

(d) Peptide map

Selective fragmentation of the product into discrete peptides is performed using suitable enzymes or chemicals, and the resulting peptide fragments are analyzed by high pressure liquid chromatography (HPLC) or other appropriate analytical procedures. The peptide fragments should be identified to the extent possible using techniques such as amino acid compositional analysis, N-terminal sequencing, or mass spectrometry. Peptide mapping of the drug substance or drug product using an appropriately validated procedure is a method that is frequently used to confirm desired product structure for lot release purposes.

(e) Sulfhydryl group(s) and disulfide bridges

If, based on the gene sequence for the desired product, cysteine residues are expected, the number and positions of any free sulfhydryl groups and/or disulfide bridges should be determined, to the extent possible. Peptide mapping (under reducing and nonreducing conditions), mass spectrometry, or other appropriate techniques may be useful for this evaluation.

(f) Carbohydrate structure

For glycoproteins, the carbohydrate content (neutral sugars, amino sugars, and sialic acids) is determined. In addition, the structure of the carbohydrate chains, the oligosaccharide pattern (antennary profile), and the glycosylation site(s) of the polypeptide chain are analyzed, to the extent possible.

6.1.2 Physicochemical properties

(a) Molecular weight or size

Molecular weight (or size) is determined using size exclusion chromatography, sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (under reducing and/or nonreducing conditions), mass spectrometry, and other appropriate techniques.

(b) Isoform pattern

This is determined by isoelectric focusing or other appropriate techniques.

(c) Extinction coefficient (or molar absorptivity)

In many cases, it will be desirable to determine the extinction coefficient (or molar absorptivity) for the desired product at a particular ultraviolet (UV)/visible wavelength (e.g., 280 nanometers). The extinction coefficient is determined using UV/visible spectrophotometry on a solution of the product having a known protein content as determined by techniques such as amino acid compositional analysis or nitrogen determination. If UV absorption is used to measure protein content, the extinction coefficient for the particular product should be used.

(d) Electrophoretic patterns

Electrophoretic patterns and data on identity, homogeneity, and purity can be obtained by polyacrylamide gel electrophoresis, isoelectric focusing, SDS-polyacrylamide gel electrophoresis, Western-blot, capillary electrophoresis, or other suitable procedures.

(e) Liquid chromatographic patterns

Chromatographic patterns and data on the identity, homogeneity, and purity can be obtained by size exclusion chromatography, reverse-phase liquid chromatography, ion-exchange liquid chromatography, affinity chromatography, or other suitable procedures.

(f) Spectroscopic profiles

The UV and visible absorption spectra are determined as appropriate. The higher-order structure of the product is examined using procedures such as circular dichroism, nuclear magnetic resonance (NMR), or other suitable techniques as appropriate.

6.2 Appendix for Impurities

This appendix lists potential impurities, their sources, and examples of relevant analytical approaches for detection. Specific impurities and technical approaches employed, as in the case of physicochemical characterization, will vary from product to product, and alternative approaches other than those listed in this appendix will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed and should be applied when appropriate.

6.2.1 Process-related impurities and contaminants

These are derived from the manufacturing process (section 2.1.4) and are classified into three major categories: Cell substrate-derived, cell culture-derived and downstream-derived.

(a) Cell substrate-derived impurities include, but are not limited to, proteins derived from the host organism and nucleic acid (host cell genomic, vector, or total DNA). For host cell proteins, a sensitive assay, e.g., immunoassay, capable of detecting a wide range of protein impurities is generally utilized. In the case of an immunoassay, a polyclonal antibody used in the test is generated by immunization with a preparation of a production cell minus the

product-coding gene, fusion partners, or other appropriate cell lines. The level of DNA from the host cells can be detected by direct analysis on the product (such as hybridization techniques). Clearance studies, which could include spiking experiments at the laboratory scale, to demonstrate the removal of cell substrate-derived impurities such as nucleic acids and host cell proteins may sometimes be used to eliminate the need for establishing acceptance criteria for these impurities.

(b) Cell culture-derived impurities include, but are not limited to, inducers, antibiotics, serum, and other media components.

(c) Downstream-derived impurities include, but are not limited to, enzymes, chemical and biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidizing and reducing agents), inorganic salts (e.g., heavy metals, arsenic, nonmetallic ion), solvents, carriers, ligands (e.g., monoclonal antibodies), and other leachables.

For intentionally introduced, endogenous, and adventitious viruses, the ability of the manufacturing process to remove and/or inactivate viruses should be demonstrated as described in ICH guidance ''Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin.''

6.2.2 Product-related impurities including degradation products

The following represents the most frequently encountered molecular variants of the desired product and lists relevant technology for their assessment. Such variants may need considerable effort in isolation and characterization in order to identify the type of modification(s). Degradation products arising in significant amounts during manufacture and/or storage should be tested for and monitored against appropriately established acceptance criteria.

(a) Truncated forms. Hydrolytic enzymes or chemicals may catalyze the cleavage of peptide bonds. These may be detected by HPLC or SDS–PAGE. Peptide mapping may be useful, depending on the property of the variant.

(b) Other modified forms. Deamidated, isomerized, mismatched S–S linked, oxidized, or altered conjugated forms (e.g., glycosylation, phosphorylation) may be detected and characterized by chromatographic, electrophoretic, and/or other relevant analytical methods (e.g., HPLC, capillary electrophoresis, mass spectroscopy, circular dichroism).

(c) Aggregates. The category of aggregates includes dimers and higher multiples of the desired product. These are generally resolved from the desired product and product-related substances and quantitated by appropriate analytical procedures (e.g., size exclusion chromatography, capillary electrophoresis).

Dated: August 11, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–21352 Filed 8–17–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99D–2636]

Draft Guidance for Industry on Levothyroxine Sodium; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ''Levothyroxine Sodium.'' The draft guidance is intended to answer questions concerning applications for orally administered levothyroxine sodium drug products.

DATES: Written comments on the draft guidance may be submitted by October 18, 1999. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Copies of this draft guidance are available on the Internet at ''http://www.fda.gov/cder/guidance/index.htm''. Submit written requests for single copies of the draft guidance for industry to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFD–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a draft guidance for industry entitled ''Levothyroxine Sodium.'' In the **Federal Register** of August 14, 1997 (62 FR 43535), FDA announced that orally administered levothyroxine sodium drug products are new drugs. The notice stated that manufacturers who wish to continue to market these products must submit applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) and 21 CFR part 314. The notice stated that FDA is prepared to accept new drug applications for these products, including applications under section 505(b)(2) of the act. A number of questions have arisen with respect to applications for levothyroxine sodium. This draft guidance is intended to answer questions about submitting applications for orally administered levothyroxine sodium drug products.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices (62 FR 8961, February 27, 1997). The draft guidance represents the agency's current thinking on issues concerning applications, including applications under section 505(b)(2) of the act, for levothyroxine sodium. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may submit written comments on the draft guidance to the Dockets Management Branch (address above). 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. The draft guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: August 9, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–21353 Filed 8–17–99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Human Genome Research Institute; Notice of Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the National Advisory Council for Human Genome Research.

The meeting will be open to the public as indicated below, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and/or contract proposals and the discussions could disclose confidential