TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Form No.	21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Form FDA 356 V	514.1 and 514.6	190	6.76	1,824	211.6	271,694
	514.8 and 514.9				30	8,520
	514.11				1	1,824
Total burden hours						282,038

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

The estimate of the burden hours required for reporting are based on fiscal year 1996 data. The burden estimate includes original NADA's, supplemental NADA's, and amendments to unapproved applications.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–15271 Filed 6–8–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Request for Nominations for Members on Public Advisory Committees; Veterinary Medicine Advisory Committee

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting nominations for members to serve on the Veterinary Medicine Advisory Committee (the Committee) in FDA's Center for Veterinary Medicine.

FDA has a special interest in ensuring that women, minority groups, and the physically challenged are adequately represented on advisory committees and, therefore, extends particular encouragement to nominations for appropriately qualified candidates from these groups.

DATES: No cutoff date is established for receipt of nominations.

ADDRESSES: All nominations for membership should be submitted to Jacquelyn L. Pace (address below).

FOR FURTHER INFORMATION CONTACT: Jacquelyn L. Pace, Center for Veterinary Medicine (HFV–200), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6650.

SUPPLEMENTARY INFORMATION: FDA is requesting nominations for members to serve on the Committee. The function of the Committee is to review and evaluate available data concerning safety and effectiveness of marketed and investigational new animal drugs, feeds, and devices for use in the treatment and prevention of animal disease and increased animal production.

Criteria for Members

Persons nominated for membership on the Committee shall have adequately diversified experience that is appropriate to the work of the Committee in such fields as companion animal medicine, food animal medicine, avian medicine, microbiology, biometrics, toxicology, pathology, pharmacology, animal science, public health/epidemiology, minor species/minor use veterinary medicine, and chemistry. The specialized training and experience necessary to qualify the nominee as an expert suitable for appointment is subject to review, but may include experience in medical practice, teaching, and/or research relevant to the field of activity of the Committee. The term of office is 4 years.

As of November 1, 1998, the Committee will have three vacancies in the areas of animal science, veterinary toxicology, and veterinary microbiology. However, membership nominations are not limited to these three areas.

Nomination Procedures

Any interested person may nominate one or more qualified persons for membership on the Committee. Nominations shall state that the nominee is willing to serve as a member of the Committee and appears to have no conflict of interest that would preclude committee membership. A current copy of the nominee's curriculum vitae should be included. Potential candidates will be asked by FDA to provide detailed information concerning such matters as employment, financial holdings, consultancies, and research grants or contracts in order to permit evaluation of possible sources of conflict of interest.

This notice is issued under the Federal Advisory Committee Act (5 U.S.C. app. 2) and 21 CFR part 14, relating to advisory committees.

Dated: May 29, 1998.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 98–15195 Filed 6–8–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D–0374]

International Conference on Harmonisation; Draft 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 draft guidance entitled ''Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.'' The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft 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 draft 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: Written comments by July 24, 1998.

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft 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), 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:

Regarding the guidance: 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 the 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 February 1998, the ICH Steering Committee agreed that a draft guidance entitled ''Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products'' should be made available for public comment. The draft guidance is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group.

The draft 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 draft 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 draft guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological/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.

Interested persons may, on or before July 24, 1998, submit to the Dockets Management Branch (address above) written comments on the draft guidance. 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. An electronic version of this draft 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 draft guidance follows:

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

Table of Contents

1.0 Introduction

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria with 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 their manufacture should conform to be considered acceptable for their intended use.

[1] This draft guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological/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.

''Conformance to specification'' means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are proposed and justified by the manufacturer, and approved by regulatory authorities.

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, 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.

1.1 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/biological products to support new marketing applications.

1.2 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/polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components.

This document does not recommend specific test procedures or acceptance criteria that should be established for the proposed value, nor does it apply to the regulation of preclinical and/or clinical research material.

2.0 General Principles for Consideration in Setting Specifications

2.1 Characterization

Characterization of a biotechnological/biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) 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/clinical studies, data from lots used for demonstration of manufacturing consistency, and relevant development data, such as those arising from analytical procedures and stability studies.

Extensive characterization usually is performed only 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 (primary and working) which will serve for biological assay and physicochemical testing of production lots.

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 has 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/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 during 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. Such technologies 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 which describes the specific ability or capacity of a product to achieve its intended 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/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. Although mimicking the biological activity in the clinical situation is not necessary, a correlation between the expected clinical response and the activity in the biological assay should be established.

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 correlates 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/drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., 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/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 have properties comparable to the desired product, they are considered product-related substances and not impurities (see 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/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 isolated, the identity of these materials should be determined as a minimum requirement and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, i.e., derived from the culture (e.g., inducers, antibiotics, or media components) or from downstream processing (see appendix section 6.2.1). Product-related impurities (e.g., certain degradation products) are molecular variants arising from processing or during storage, which 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 for 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. Such technologies 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/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 or drug substance/drug product specifications (see 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/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 measurement of biological activity to determine manufacturing parameters, such as for 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/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/drug product which 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 on 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 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 points where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The in-process test results may be recorded as action limits or reported as acceptance criteria. Monitoring for the presence of mycoplasma and adventitious virus at the end of a cell culture harvest and/or other stages is an example of testing for which in-process acceptance criteria should be set. Performing

such testing may eliminate the need for testing of the drug substance/drug product (section 2.3.1).

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, should be further refined as increased 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 acceptable 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/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/biological products, generally include, but are not limited to, tests for sterility, endotoxins, bioburden, volume in container, uniformity of dosage forms, 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/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/validation, 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/clinical studies, lots used for demonstration of manufacturing consistency, and relevant development data, such as those arising from analytical procedures and stability studies.

In some cases, testing at production stages rather than testing the finished drug substance or drug product 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. 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/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 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) for a drug substance can be qualitative in nature and, generally, need not be highly sensitive. 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

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

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 culture media, host cell proteins, DNA,

monoclonal antibodies and chromatographic media used in purification, solvents/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 resulting from processing or from storage.

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.

4.1.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biological/biotechnological drug substance and/or drug product. When an appropriate potency assay is used for the drug product, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage (section 4.2.4). 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 reference standard/material independent. 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 forms, and moisture content for lyophilized drug products. If appropriate, testing for uniformity of dosage form may be performed as in-process controls and corresponding acceptance criteria are set.

4.2.1 Appearance/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 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 and generally need not be highly sensitive. 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 increase in the manufacture 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 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 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 excipients and impurities including degradation products inherent in the drug product.

4.2.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biological/biotechnological 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 (section 4.1.4).

4.2.5 Quantity

The quantity of the drug substance in the drug product, usually based on protein content, 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 which the drug substance or drug product or materials at other stages of their manufacture should meet to conform with the specification of the results of analytical procedures.

Action limits: An action limit is an internal (in-house) value used to assess the consistency of the process at less critical steps. These limits are the responsibility of the manufacturer.

Biological activity: Biological activity describes the specific ability or capacity of the product to achieve its intended biological effect. Potency is the quantitative measure of the biological activity.

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

Degradation products: Degradation products are 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 processing and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

Desired product: The protein that is expected from the DNA sequence and anticipated post-translational modifications (including glycoforms) and intended downstream processing necessary 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 drug substance is the material which 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 and other components, such as buffers.

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

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 added buffer components). It may be either process- or product-related.

Potency: Potency is 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, culture (e.g., inducers, antibiotics, or media components), or from downstream processing (e.g., processing reagents or column leachables).

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

Product-related substances: Product-related substances are molecular variants of the desired product 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.

Raw material: Raw material is a collective name for substances or components used in the manufacture of the drug substance or drug product.

Reference standards/materials: In addition to the existing international/national standards, it is usually necessary to create in-house reference materials.

— *In-house primary reference material*: A primary reference material is 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*: The in-house working reference material is a material prepared similarly to the primary reference material and 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.

Specification: A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria for the tests described, which establishes the set of criteria to which a drug substance or drug product or materials at other stages of their manufacture should conform to be considered acceptable for its intended use.

6.0 Appendices

6.1 Appendix for Physicochemical Characterization

This appendix provides examples of technical approaches which might be considered for structural characterization/confirmation and evaluation of physicochemical properties of the desired 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. Such technologies should be utilized when appropriate.

6.1.1 Structural characterization/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 protein, or the natural counterpart, if considered necessary, taking into account the size of the molecule. 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 (N-) and carboxy (C)-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 protein.

(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 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. Validated peptide mapping is frequently an appropriate method to confirm desired product structure/identity for lot release purposes.

(e) Sulfhydryl group(s) and disulfide bridges

If, based on the gene sequence for the desired protein, 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 acid) 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/size

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

(b) Isoform pattern

This is determined by isoelectrical 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 UV/visible wavelength (e.g., 280 nanometers). The extinction coefficient is determined using UV/visible spectrophotometry on a solution having a known protein content as determined by techniques such as amino acids compositional analysis or nitrogen determination.

(d) Electrophoretic patterns

Electrophoretic patterns and data on identity, homogeneity, and purity of the desired product/drug substance obtained by polyacrylamide gel electrophoresis, isoelectric focusing, SDS-polyacrylamide gel electrophoresis, Western-Blot, capillary electrophoresis, or other suitable procedures are determined as appropriate.

(e) Liquid chromatographic patterns

Chromatographic patterns and data on the identity, homogeneity, and purity of the desired product/drug substance obtained by size exclusion chromatography, reverse-phase liquid chromatography, ion-exchange liquid chromatography, affinity chromatography, or other suitable procedures are determined as appropriate.

(f) Spectroscopic profiles

The ultraviolet 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. Such technologies should be utilized when appropriate.

6.2.1 Process-related impurities

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

(a) Cell substrate-derived impurities include proteins/polypeptides derived from the host organism; nucleic acid (host cell generic/vector/total DNA); polysaccharides; viruses. For host cell proteins, a sensitive immunoassay capable of detecting a wide range of protein impurities is generally utilized. The polyclonal antibody utilized in the test is generated from a crude preparation of a mock production organism, i.e., a production cell minus the product-coding gene. The level of DNA from host cells can be detected by direct analyses on the product (such as hybridization techniques) and/or by spiking experiments (laboratory scale) demonstrating the removal of nucleic acid by the purification process. For intentionally introduced viruses, the ability of the manufacturing process to remove/inactivate viruses should be demonstrated as described in the ICH guidance Q5A ''Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.''

(b) Culture-derived impurities include inducers (polynucleotides, viruses) antibiotics, serum, other media components.

(c) Downstream-derived impurities include enzymes, chemical/biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidizing and reducing agents), inorganic salts (e.g., heavy metals, arsenic, non metallic ion), solvents, carrier/ligands (e.g., monoclonal antibodies), other leachables.

6.2.2 Product-related impurities

The following represents the most frequently encountered molecular variants of the desired product and lists relevant technology for their assessment:

(a) Truncated forms. Cellular peptidases may catalyze the removal of amino acids or catalyze internal cleavages. This may be detected by HPLC or SDS–PAGE. Peptide mapping may be useful, depending on the property of the variant.

(b) Deamidated, isomerized, mismatched S–S linked, oxidized forms may need considerable effort in isolation and characterization in order to identify the type of chemical modification(s) and amino acid residue(s) involved. Chromatographic and/or electrophoretic methods (e.g., HPLC, capillary electrophoresis, mass spectroscopy, circular dichroism) may be utilized to isolate and characterize such variants.

(c) The category of aggregates includes dimers and higher multiples of the molecular entity. These are generally resolved from the active moiety and quantitated by size exclusion chromatography (e.g., SE–HPLC). Degradants identified from stability studies as being generated in significant amounts should be tested for and monitored against appropriately established acceptance criteria.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–15193 Filed 6–8–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98N–0285]

Sanofi Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 21 New Drug Applications and 62 Abbreviated New Drug Applications; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a document that appeared in the **Federal Register** of May 12, 1998 (62 FR 26191). The document announced the withdrawal of approval of 21 new drug applications (NDA's) and 62 abbreviated new drug applications (ANDA's). The document was published with an error in the identification of NDA for Pipanol Powder and Tablets (trihyphenidyl) held by Sanofi Pharmaceuticals, Inc. This document corrects that error.

EFFECTIVE DATE: June 11, 1998.

FOR FURTHER INFORMATION CONTACT: Olivia A. Pritzlaff, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

In FR Doc. 98–12613, appearing on page 26191 in the **Federal Register** of Tuesday, May 12, 1998, the following correction is made:

On page 26191, in the table, in the first column, the first entry ''NDA 4–496'' is corrected to read ''NDA 7–796''.

Dated: June 3, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–15338 Filed 6–8–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N–0532]

Agency Information Collection Activities; Announcement of OMB Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled ''Radioactive Drug Research Committee (RDRC) Report on Research Use of Radioactive Drug Membership Summary and Radioactive Drug Research Use of Radioactive Drug Study Summary'' has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA).

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 9, 1998 (63 FR 1484), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under section 3507 of the PRA (44 U.S.C. 3507). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910–0053. The approval expires on May 31, 2001.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–15191 Filed 6–8–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[HCFA–1044–N]

Medicare Program; June 22, 1998, Meeting of the Practicing Physicians Advisory Council

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice of meeting.

SUMMARY: In accordance with section 10(a) of the Federal Advisory Committee Act, this notice announces a meeting of the Practicing Physicians Advisory Council. This meeting is open to the public.

DATES: The meeting is scheduled for June 22, 1998, from 8:30 a.m. until 5 p.m., E.S.T.

ADDRESSES: The meeting will be held in Room 800, 8th Floor, Hubert H. Humphrey Building, 200 Independence Avenue, SW, Washington, DC 20201.

FOR FURTHER INFORMATION CONTACT: Aron Primack, MD, MA, FACP, Executive Director, Practicing Physicians Advisory Council, Room 435–H, Hubert H. Humphrey Building, 200 Independence Avenue, S.W., Washington, DC 20201, (202) 690–7874

SUPPLEMENTARY INFORMATION: The Secretary of the Department of Health and Human Services (the Secretary) is mandated by section 1868 of the Social Security Act to appoint a Practicing Physicians Advisory Council (the Council) based on nominations submitted by medical organizations representing physicians. The Council meets quarterly to discuss certain proposed changes in regulations and carrier manual instructions related to physicians' services, as identified by the Secretary. To the extent feasible and consistent with statutory deadlines, the consultation must occur before publication of the proposed changes. The Council submits an annual report on its recommendations to the Secretary and the Administrator of the Health