and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

Interested persons may, on or before October 5, 1995, submit to the Dockets Management Branch (address above) written comments on the draft guideline. 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 guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility

1. Introduction

1.1 Objective

Addendum to ICH—S5A Tripartite Guideline

1.2 Male fertility investigation, as included in the currently harmonized guideline, was accepted to recommend scientific and regulatory improvement and optimization of test designs.

1.3 Better description is needed of the testing concept and recommendations with regard to male fertility assessment, especially those addressing:

- Flexibility
- Premating treatment duration
- Observation

1.4 The general principles and background are contained in two papers accepted for publication to the *Journal of American College of Toxicology*.

These papers contain necessary experimental data (prospective and retrospective) for reaching consensus, and have been discussed among the expert working group. The ''raw data'' from the Japanese study will also be published.

1.5 The projected timeframe proposed:

—Step 2 in Washington, March 1995
—Step 3 in Brussels, July 1995
—Step 4 in Yokohama, November 1995

2. The guideline draft texts are attached.

3. For glossary see the harmonized S5—A guideline

Introduction

(Last paragraph revised)

To employ this concept successfully, flexibility is needed (Note 1). No guideline can provide sufficient information to cover all possible cases. All persons involved should be willing to discuss and consider variations in test strategy according to the state-of-the-art and ethical standards in human and animal experimentation. (*Delete next sentence*)

Note 12 (4.1.l) Premating Treatment

(Revised)

The design of the fertility study, especially the reduction in the premating period for males, is based on evidence accumulated and reappraisal of the basic research on the process of spermatogenesis. Compounds inducing selective effects on male reproduction are rare; compounds affecting spermatogenesis almost invariably affect postmeiotic stages; mating with females is an insensitive means of detecting effects on spermatogenesis. Histopathology of the testis has been shown to be the most sensitive method for the detection of effects on spermatogenesis. Good pathological and histopathological examination (e.g., by employing Bouin's fixation, paraffin embedding, transverse section of 2 to 4 microns for testes, longitudinal section for epididymides, PAS, and haematoxylin staining) of the male reproductive organs provides a quick direct means of detection. Sperm analysis (sperm counts and optionally sperm motility, sperm morphology) can be used as a method to confirm findings by other methods and to characterize effects further. Sperm are derived from the more mature stages. Samples from ejaculates, from vas deferens, or from cauda epididymis should be used. Information on potential effects on spermatogenesis (and female reproductive organs) can be derived from repeated dose toxicity studies.

For detection of effects unrelated to spermatogenesis (sperm abnormalities, mating behavior), mating with females after a premating treatment of 2 and 4 weeks has been shown to be at least as efficient as mating after a longer duration of treatment. When the available evidence suggests that the scope of investigations in the fertility study should be increased, appropriate studies should be designed to characterize the effects further.

Administration Period

(Revised)

The design assumes that, especially for effects on spermatogenesis, use will be made of data (e.g., histopathology and weight of reproductive organs, hormone assays, and genotoxicity data) from repeated dose toxicity studies. Provided no effects have been found that preclude this, a premating treatment interval of 2 weeks for females and 4 weeks for males (2 weeks may be acceptable in some cases) can be used (Note 12). Selection of the length of the premating administration period should be stated and justified (see also chapter 1.1, pointing out the need for research). Treatment should continue throughout mating to termination for males and at least through implantation for females. This will permit evaluation of functional effects on male fertility that cannot be detected by histologic examination in repeated dose toxicity studies and effects on mating behavior in both sexes. If data from other studies show there are effects on weight or histologic appearance of reproductive organs in males or females, or if the quality of examinations is dubious, or if there are no data from other studies, then a more comprehensive study should be designed (Note 12).

4.1.1 Study of Fertility and Early Embryonic Development to Implantation

Observations

(Revised)

At terminal examination, the following observations should be made:

- Necropsy (macroscopic examination) of all adults;
- Preserve organs with macroscopic findings for possible histological evaluation; keep corresponding organs of sufficient controls for comparison;
- Preserve testes, epididymides, ovaries, and uteri from all animals for possible histological examination and evaluation on a case-by-case basis;
- Count corpora lutea, implantation sites (Note 16);
- Live and dead conceptuses; and
- Sperm analysis as an optional procedure for confirmation or better characterization of an effect observed (Note 12).

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20609 Filed 8–18–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93D–0139]

International Conference on Harmonisation; Draft Guideline on Stability Testing of Biotechnological/ Biological Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.'' This draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications for biotechnological/ biological products.

DATES: Written comments by October 5, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, as well as the CBER Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research,

Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Kenneth Seamon, Center for Biologics Evaluation and Research (HFM–20), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0375.

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.

At a meeting held on March 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products'' should be made available for public comment. The draft guideline is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's final guideline.

This draft guideline is intended to supplement the tripartite ICH guideline entitled ''Stability Testing of New Drug Substances and Products,'' published in the **Federal Register** of September 22, 1994 (59 FR 48754). Biotechnological/biological products have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products, in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and biological activity is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, shear, etc. In order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary. This draft guideline is intended to assist the applicant in developing appropriate supporting stability data for a biotechnological/biological product.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

Interested persons may, on or before October 5, 1995, submit written comments on the draft guideline 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 guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C)

ICH Expert Working Group on Quality of Biotechnology Products

Annex to the Tripartite ICH Guideline for the Stability Testing of New Drug Substances and Products

Introduction

The principles established in the ICH harmonized tripartite guideline ''Stability Testing of New Drug Substances and Products'' (27 October 1993) apply in general to biotechnological/biological products. However, biotechnological/biological products do have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products, in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence of biological activity, is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, shear, etc. In order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, are an essential part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With the above concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions which can affect the product's potency, purity, and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

Scope of the Annex

The principles adopted and explained in this annex apply to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the

generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the principles outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities.

The document does not cover antibiotics, allergenic extracts, heparins, vitamins, or whole blood.

Terminology

For the basic terms used in this annex the reader is referred to the ''Glossary'' in the ICH harmonized tripartite guideline ''Stability Testing of New Drug Substances and Products'' (27 October 1993). However, since traditional terminology used by manufacturers of biotechnological/biological products does not always conform to that of the tripartite guideline mentioned above, traditional terms are specified in brackets to assist the reader. A supplemental glossary is also included that defines certain of the traditional terms used in the biologics field.

Selection of Batches

Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture but prior to formulation and final manufacturing, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of 6 months stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug substances with storage periods of less than 6 months, the minimum amount of stability data in the initial submission will be determined on a case-by-case basis. Data from pilot-plant-scale batches of a well-characterized drug substance (bulk material) produced at a reduced scale of fermentation and purification may be provided at the time the dossier is submitted to the regulatory agencies with a commitment to place the first three full-scale batches into the long-term stability program after approval.

The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the drug substance (bulk material) made at pilot-plant scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale. The drug substance entered into the stability program should be stored in containers which properly represent the actual holding containers used during manufacture. Scaled-down containers may be acceptable for drug substance stability monitoring assuming that they are constructed of the same material and make use of the same type of container/closure system that is routinely used during the manufacture.

Intermediates

During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process. While the use of pilot-plant-scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing-scale process.

Drug Product (Final Container Product)

Stability information should be provided on at least three batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of 6-months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission will be reviewed on a case-by-case basis. Product expiration dating will be based upon the actual data submitted in support of the application. Since dating is based upon the real-time/real-temperature data submitted for review, it is expected that continuing updates of initial stability data will occur during the review and evaluation process. Where pilot-scale batches were submitted to establish the dating for a product and, in the event that product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating period or is not representative of the material used in preclinical and clinical studies, the sponsor/applicant should notify the appropriate regulatory authorities to determine a suitable course of action.

Sample Selection Criteria

Where one product is distributed in batches differing in fill volume (e.g., 1 milliliter (mL), 2 mL, or 10 mL), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 milligram (mg), 2 mg, or 5 mg) samples to be entered into the stability program may be selected on the basis of a matrix system and/or by bracketing.

Matrixing, i.e., the statistical design of a stability study in which different fractions of samples are tested at different sampling points, should only be applied when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same closure and possibly, in some cases, different container/closure systems. Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers/closures, where it cannot be confirmed that the products respond similarly under storage conditions.

Where the same strength and exact container/closure system is used for three or more fill contents, the applicant may elect to place only the smallest and largest container size into the stability program, i.e., bracketing. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples are represented by those at the extremes. In certain cases, it may be necessary to provide data that demonstrate that all samples are properly represented by data collected for the extremes.

Stability-Indicating Profile

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

It is also expected that, at the time of submission, applicant/firms have validated the methods that comprise the stability-indicating profile and that the data are available for review. The determination of which tests should be included will be product specific. The items emphasized in the following subsections are not intended to be all inclusive, but represent product characteristics that should typically be documented to demonstrate product stability adequately.

Protocol

The dossier accompanying the application for marketing authorization should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the claimed storage conditions and expiration dating periods. The protocol should include all necessary information, including well-defined specifications, test intervals, etc., which taken as a whole, demonstrates the stability of the biotechnological/biological product throughout the claimed expiration dating period. The statistical methods to be used are described in the tripartite guideline. It is assumed that the manufacturer of the product will strictly adhere to this protocol.

Potency

Wherever the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. Potency studies should be performed at appropriate intervals as defined in the stability protocol and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standards. Where no national or international agreement has been reached on units of potency, the assay results may be reported in in-house derived units using an appropriately characterized reference preparation.

In some biotechnological/biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active ingredient(s) from the carrier used in conjugates or adjuvants

should be examined in real-time/real-temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be associated with difficulties since, in some cases, in vitro tests for biological activity and physicochemical characterisation are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product prior to conjugation/binding, release of the active compound from the second moiety, in vivo assays, etc.) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

Purity and Molecular Characterization

The degree of purity, as well as individual and total upper limits for degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

For physicochemically well-defined drug substances and/or drug products, the use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterisation of the active ingredient (e.g., molecular size, charge, hydrophobicity, etc.) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography, etc.), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity level cannot be meaningfully determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/biological products, should be monitored and reported for the drug product in its final container:

Visual appearance of the product (colour and opacity for solutions/suspensions; colour, texture, and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.

Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

Additives (stabilizers, preservatives, etc.) or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely affect the quality of the drug product, these items may need to be monitored during the stability program.

The container/closure has the potential to adversely affect the product and should be carefully evaluated. Closure configurations, vial liners seal-types should also be considered (see below).

Storage Conditions

Temperature

Since most finished biotechnological/biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the recommended storage temperature.

Humidity

Biotechnological/biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

Accelerated and Stress Conditions

As previously noted, the expiration dating generally is based upon the real-time/real-temperature data. However, it is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up, etc.), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those recommended (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under recommended storage conditions. While the tripartite guideline describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.

Light

Applicants should consult the appropriate regulatory authorities on a case-by-case basis to determine guidance for testing.

Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/biological product and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container/closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

Stability After Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

Testing Frequency

The shelf-lives of biotechnological/biological products may vary from days to several years. Thus, it is difficult to draft uniform guidelines regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological/biological products. With only a few exceptions, however, the shelf-lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the recommendations that follow are based upon expected shelf-lives in that range, and take account of the fact that, frequently, degradation of biotechnological/biological products is not governed by the same factors during different intervals of a long storage period.

When shelf lives of 1 year or less are proposed, the real-time stability studies generally should be conducted monthly for the first 3 months and at 3-month intervals thereafter.

For products with proposed shelf-lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

While the testing intervals listed above are appropriate in the preapproval or prelicense stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol that supports elimination of specific test intervals (e.g., 9-month testing) for postapproval/postlicensure, long-term studies.

Specifications

Although biotechnological/biological products may be subject to significant losses of activity and to physicochemical degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end-of-shelf-life specifications. Recommendations for maximum acceptable losses of activity or limits for physicochemical changes (degradation) during the proposed shelf-life have not been developed for individual types or groups of biotechnological/biological products but are considered on a case-by-case basis. Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf-life. These specifications and limits should be derived from all available information using the appropriate statistical methods. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected. The proposals should be in accordance with the principles outlined in the appropriate section of the tripartite guideline.

Labeling

For most biotechnological/biological drug substances and drug products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for drug substances and drug products that cannot tolerate freezing. These conditions, and where appropriate, recommendations for protection against light and/or humidity, should appear on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

Glossary

Conjugated Product

A conjugated product is made up of an active ingredient (peptide, carbohydrate, etc.) bound covalently or noncovalently to a carrier (protein, peptide, inorganic mineral, etc.) with the objective of improving the efficacy or stability of the product.

Degradation Product

Any material resulting from modification of the active ingredients, additives, and/or excipients present in a drug substance or drug product which occurs due to processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis, etc.). Degradation products are considered impurities, although some degradation products may be active.

Impurity

Any process-generated substance present in raw materials, drug substance, or drug product that is not considered to be active ingredient, additives, or excipients.

Intermediate

A material produced during a manufacturing process that is not the drug substance or the drug product but whose manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications will be established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes material that may undergo further molecular modification or be held for an extended period of time prior to further processing.

Manufacturing-Scale Production

Manufacture at the scale typically encountered in a facility at the largest capacity intended for product production for marketing.

Pilot-Plant Scale

The production of the drug substance or drug product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Potency

Expression of the predicted capacity of a product to achieve its intended role; it is based on the measurement of some attribute of the product and is determined by a suitable quantitative laboratory method. In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an appropriate reference material. For that purpose a reference material calibrated directly or indirectly against the corresponding national or international reference material is included in the assay. The reference material should have some known relationship with the product, the therapeutic, preventive, or diagnostic capacity of which has been studied in humans.

Purity

Purity is a relative term with respect to biotechnological/biological products. The purity may be expressed as the amount (weight/weight) of the desired protein of a homogeneous amino acid sequence usually expressed on a percentage basis. However, due to the effects of glycosylation, deamidation, etc., the absolute purity of a biotechnological/biological product is extremely difficult to determine. Therefore, the purity of biotechnological/biological products may be evaluated by determining the amounts of known impurities, such as host cell proteins, DNA, other impurities, and/or degradation products. Thus, the purity of a biotechnological/biological product is typically assessed by more than one method and the purity value derived is method-dependent. For example, the purity values derived from a chromatographic and by an electrophoretic method may be different but equally valid for a given batch of biotechnological/biological product because each method focuses on a different aspect of this biological entity.

Well-Characterized (Biotechnological/Biological) Product

A product whose structural features (including amino acid sequences, as well as physicochemical, biochemical, biological and/or immunochemical properties) have been elucidated using a set of modern, bioanalytical, and testing methods.

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20608 Filed 8–18–95; 8:45 am]

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