product, which require submission of a supplement and approval by FDA prior to distribution of the product made using the change; 2) changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change; and 3) changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product, which are to be described by the applicant in an annual report.

Under §601.12(f), changes to a product package label, container label, and package insert require either: (1) submission of a supplement with FDA approval needed prior to product distribution; (2) submission of a supplement with product distribution allowed at the time of submission of the supplement; or (3) submission of the final printed label in an annual report.

Under § 601.12(f)(4), changes to advertising and promotional labeling must be made in accordance with the provisions of 21 CFR 314.81(b)(3)(i), which requires the submission to FDA of specimens of mailing pieces and any other labeling or advertising devised for promotion of a drug product at the time of initial dissemination of the labeling, and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted from the container. Each submission to CBER should be accompanied by a completed transmittal Form FDA-2567, or, when it is made available, the revised Form FDA-2253.

This guidance applies to all licensed biological products, including Whole Blood, blood components, Source Plasma, and Source Leukocytes, but not including the specified biotechnology and specified synthetic biological products listed in 21 CFR 601.2(c) (see Guidance to Industry - Changes To An Approved Application For Specified Biotechnology And Specified Synthetic Biological Products), and to all licensed establishments, including contract locations. This guidance is intended to assist manufacturers in determining which reporting mechanism is appropriate for a change to an approved license application.

In addition to the requirements in 21 CFR 601.12, an applicant making a change to an approved license application must conform to other applicable law and regulations, including the current good manufacturing practice (CGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in 21 CFR parts 210, 211, 600 through 680, and 820. For example, manufacturers must comply with record-keeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

Under each subsection of this guidance, FDA describes a category of changes to be reported under § 601.12. FDA also provides a listing of various changes that FDA currently believes fall under each category. Additional changes applicable only to Whole Blood, blood components, Source Plasma, and Source Leukocytes are listed separately. A separate section on labeling describes those labeling

changes to be submitted as supplements requiring prior approval, supplements submitted at the time the change is made, and submission in an annual report.

II. CHANGES UNDER §601.12(b) - Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

Under §601.12(b), changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement and approval by FDA before a product made using the change is distributed. For a change under this category, an applicant is required to submit a supplement to the approved license application that includes a detailed description of the proposed change; the products involved; the manufacturing site(s) or area(s) affected; a description of the methods used and studies performed to evaluate the effect of the change on the product's identity, strength, quality, purity, and potency of the product as they may relate to its safety or effectiveness; the data derived from those studies; relevant validation protocols and data; and a reference list of relevant standard operating procedures (SOPs). As noted, the applicant must obtain approval of the supplement by FDA prior to distribution of the product made using the change.

In FDA's experience, the following changes to a product, production process, quality controls, equipment, facilities, or responsible personnel have caused detrimental effects on the identity, strength, quality, purity, or potency of products as they related to the safety or effectiveness of the product even where applicants performed validation or other studies. FDA believes that these changes would generally have a substantial potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness and that the agency's continued premarket review and approval of such changes is currently necessary to protect the public from products whose identity, strength, quality, purity, potency, safety, or effectiveness may be compromised.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

1. Process changes including, but not limited to,
   - extension of culture growth time leading to significant increase in number of cell doublings beyond validated parameters;
   - new or revised recovery procedures;
   - new or revised purification process, including a change in a column;
   - a change in the chemistry or formulation of solutions used in processing;
   - a change in the sequence of processing steps or addition, deletion, or substitution of a process step; or
   - reprocessing of a product without a previously approved reprocessing protocol.

2. Any change in manufacturing processes or analytical methods that
   - results in change(s) of specification limits or modification(s) in potency, sensitivity, specificity, or purity;
   - establishes a new analytical method;
   - deletes a specification or an analytical method;
   - eliminates tests from the stability protocol; or
   - alters the acceptance criteria of the stability protocol.
3. Scale-up requiring a larger fermentor, bioreactor, and/or purification equipment (applies to production up to the final purified bulk).
4. Change in the composition or dosage form of the biological product or ancillary components (e.g., new or different excipients, carriers, or buffers).
5. New lot of, new source for, or different, in-house reference standard or reference panel (panel member) resulting in modification of reference specifications or an alternative test method.
6. Extension of the expiration dating period and/or a change in storage temperature, container/closure composition, or other conditions, other than changes based on real time data in accordance with a stability protocol in the approved license application.
7. Installation of a new Water For Injection (WFI) system; or modifications to an existing WFI system that would have a significant potential to stress or challenge the system, such as
   - lengthy or complicated distribution system extensions to service new or remote production areas;
   - use of components of lesser quality or function;
   - expansions of ambient temperature water distribution loops; or
   - conversion from hot loop to ambient loop.
8. Change of the site(s) at which manufacturing, other than testing, is performed; addition of a new location (including donor centers manufacturing platelets and/or performing automated pheresis procedures); or contracting of a manufacturing step in the approved license, to be performed at a separate facility.
9. Conversion of production and related area(s) from single to multiple product manufacturing area(s). (Addition of products to a multiple product manufacturing area could be submitted as a "Supplement - Changes Being Effected in 30 Days", if there are no changes to the approved and validated cleaning and changeover procedures and no additional containment requirements).
10. Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions.
11. Major construction, or changes in location, involving or affecting environmentally controlled manufacturing or related support areas, such as
    - new buildings;
    - new production areas or rooms in existing buildings;
    - aseptic processing areas;
    - modifications to support systems with significant potential to affect air, water, or steam quality;

- installation of a new HVAC system involving or affecting environmentally controlled manufacturing or related support areas; or
- modifications to an existing HVAC system that supplies aseptic processing areas.

Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

12. Change in SOPs in the following categories:
    a) donor suitability, including donor deferral;
    b) blood collection, including arm preparation;
    c) high risk behavior questions/AIDS information;
    d) donor history forms, including informed consent;
    e) product manufacturing; or
    f) quarantine and disposition of unsuitable product.
13. Process changes; e.g., leukoreduction; irradiation; freezing/deglycerolizing/rejuvenating; manual to automated collection of Source Plasma, Fresh Frozen Plasma, or platelets; immunization programs; disease-state (as opposed to disease-associated) or high risk donor collections.

III. CHANGES UNDER §601.12(c) - Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.

Under §601.12(c), changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement to FDA at least 30 days prior to distribution of a product made using the change. The requirements for the content of these supplements are the same as for those requiring approval prior to distribution.

Some examples of changes to the product, production process, quality controls, equipment, facilities, and responsible personnel that FDA currently considers to have moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are set forth in the following list, which FDA has developed based on experience gained in reviewing submissions received in the past.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

1. Automation of one or more process steps without a change in process methodology.
2. Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.
3. Addition or reduction in number of pieces of equipment (e.g., centrifuges, filtration devices, blending vessels, columns, etc.) to achieve a change in purification scale not associated with a process change.

4. Change in the fill volume (per vial) from an approved production batch size and/or scale (excludes going from single dose to multidose vial or change in product concentration, both of which should be submitted as a supplement requiring prior approval).
5. Changes in responsible individuals specified in the approved application, including manufacturers' representatives, responsible experts, and other individuals designated to communicate with CBER.
6. Modification of an approved manufacturing facility or room(s) that is not likely to have an adverse effect on safety, sterility assurance, purity, or potency of product; e.g., adding new interior partitions or walls to increase control over the environment.
7. Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures and there are no additional containment requirements.
8. Change in the site of testing from one facility to another (e.g., from a contract lab to the license holder; from an existing contract lab to a new contract lab; from the license holder to a new contract lab).
9. Change in the structure of a legal entity that would require issuance of new license(s), or change in name of the legal entity or location that would require reissuance of license(s).
10. Computer process control for steps to replace manual process control.
11. Downgrade of room or area environmental quality classification except for aseptic processing areas.
12. Installation of a new, or modification to an existing, Purified Water system, not including pretreatment systems for WFI.

Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

13. Change in automated collection equipment used in plasmapheresis.
14. Change in mailing address, move of a donor center at which blood components are prepared, move of an establishment, or temporary or permanent closure of a facility.
15. Off-site storage, in a location listed in the establishment license application, of product for which a supplement is pending.
16. Alternate procedure request (under §640.120) where there are published FDA recommendations/criteria.
17. Infrequent donor collection variance at blood establishment.

As described in §601.12(c)(5), in certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may determine that the product made using the change may be distributed at the time of receipt of the supplement by FDA. The following are changes that in FDA's experience have been submitted properly with the appropriate information, and could be implemented under §601.12(c)(5) at the time of receipt of the supplement by FDA without a previously approved comparability protocol.

1. Addition of release tests and/or specifications or tightening of specifications for intermediates.
2. Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product.
3. Modifications to an existing HVAC system involving or affecting environmentally controlled manufacturing or related support areas, but not aseptic processing areas, with no change in air quality.

In addition, applicants that use the protocol described in §601.12(e) to validate a proposed change may request that a change usually subject to supplement submission and approval prior to distribution be reported as a change subject to supplement submission at least 30 days prior to distribution of the product made using the change, or as a "Changes Being Effected" supplement submission, in which event the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

IV. CHANGES UNDER §601.12(d) - Changes to be described in an annual report (minor changes).

Under §601.12(d), changes to the product, production process, quality controls, equipment, facilities, or responsible personnel that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are required to be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the application. For changes under this category, the applicant is required to submit in the annual report a list of all products involved; and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, a cross-reference to relevant validation protocol(s) and/or SOPs, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Some examples of changes that FDA currently considers to have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are listed below. The list is not all-inclusive but contains items that, in FDA's experience reviewing supplements, have caused few instances in which an adverse effect on the product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness has been observed.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

1. Addition of equipment for manufacturing processes which is identical to the primary system and serves as an alternate resource within an approved production room or area.

2. Upgrade or minor corrective change to production air handling, water, or steam supply systems using equipment of same or similar materials of construction, design and operating parameters, and not affecting established specifications; e.g., removal of dead legs in water for injection (WFI) system. (Does not include replacement of parts or routine repair and maintenance which would not be changes to an approved application and would not need to be reported).
3. Relocation of analytical testing laboratories between areas specified in the license.
4. Room upgrades, such as installation of improved finishes on floors/walls.
5. Installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers.
6. Modifications in analytical procedures with no change in the basic test methodology or existing release specifications provided the change is supported by validation data.
7. Change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale.
8. Replacement of an in-house reference standard or reference panel (or panel member) according to SOPs and specifications in an approved license application.
9. Tightening of specifications for existing reference standards to provide greater assurance of product purity, identity, and potency.
10. Establishment of an alternate test method for reference standards, release panels, or product intermediates, except for release testing of intermediates licensed for further manufacture.
11. Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to an SOP on file in the approved license application.
12. Change in the storage conditions of in-process intermediates based on data from a stability protocol in an approved license application, which does not affect labeling, except for changes in storage conditions which are specified by regulation (see 21 CFR Part 640).
13. Change in shipping conditions (e.g., temperature, packaging, or custody) based on data derived from studies following a protocol in the approved license application (except for changes in shipping conditions that are required by regulation to be submitted as a supplement, see 21 CFR 600.15(b)).
14. A change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications).
15. Addition of time points to the stability protocol.
16. Replacement of equipment with that of identical design and operating principle involving no change in process parameters.
17. Upgrade in air quality, material, or personnel flow where product specifications remain unchanged. Involves no change in equipment or physical structure of production rooms.
18. Relocation of equipment within an approved operating room, rearrangement of the operating area or rooms where production is performed or relocation of equipment to another approved area to improve product/personnel/raw material flow and improve segregation of materials with no change in room air classification.

19. Modifications to the pretreatment stages of a WFI system, including Purified Water systems used solely for pretreatment in WFI production.
20. Change in the simple floor plan that does not affect production process or contamination precautions.
21. Trend analyses of release specification testing results for bulk drug substances and drug products obtained since the last annual report.

Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

22. Organizational and facilities changes which have occurred since the last report.
23. A listing of all facilities, including self-contained collection vehicles.
24. Current Organizational chart, including descriptive job titles and names. The chart should be sufficiently detailed to clearly demonstrate areas of responsibility of managerial staff.
25. List of contractual agreements in effect since the last annual report. This should contain the name of the contractor, the contractor's FDA license and/or registration number, and a description of the service or product provided. Include contractual agreements for those involved in the manufacturing process; for example, testing laboratories, contract apheresis services, contract donor collection services, suppliers of red blood cells for immunization, emergency treatment services, and short supply vendors. Contracts for blood bags, apheresis soft goods, or reagents should not be reported.
26. Change in "doing business as" name that does not affect licensed establishment name.
27. Change in computer system in conformance with FDA guidance.
28. Implementation of an FDA-approved uniform procedure (e.g., uniform donor history form or Circular of Information); implementation of FDA recommendations contained in memoranda to blood establishments.
29. Unexpected antibodies produced in immunization programs.
30. Addition of a new fixed blood collection site at which only donor suitability and Whole Blood collection are performed and for which the site is identified as an auxiliary facility to the licensed establishment on Form FDA 2830.

V. COMPARABILITY PROTOCOLS UNDER §601.12(e)

The comparability protocol described in §601.12(e) is a supplement that establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the safety and effectiveness of a product. A new comparability protocol, or a change to an existing one, requires approval prior to implementation because it may result in decreased reporting requirements for the changes covered. In general, a decrease in reporting requirement will be one reporting tier, e.g., from supplement with distribution of product in 30 days to an annual report, or from prior approval supplement to supplement with distribution of product in 30 days. In some cases the decrease may be greater. The reporting category will be established at the time that the comparability protocol is approved. FDA intends to issue further guidance on the use of such protocols in the near future.

VI. CHANGES UNDER §601.12(f) - Labeling changes.

Under §601.12(f), changes to labeling are required to be submitted to CBER in one of the following ways: (1) As a supplement requiring FDA approval prior to distribution of a product with the labeling change; (2) as a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval; or (3) in an annual report. Some examples of changes to labeling that CBER currently considers to be appropriate for submission in each of these three categories are listed below. These lists are not intended to be comprehensive. Pursuant to §601.12(f)(4), promotional labeling and advertising must be submitted to CBER at the time of initial dissemination or publication.

A. Changes under §601.12(f)(1) - Labeling changes requiring supplement submission - FDA approval must be obtained before distribution of the product with the labeling change.

Under §601.12(f)(1), any proposed change in the package insert, package label, or container label, except those described in §601.12(f)(2) and (3), is required to be submitted as a supplement and receive FDA approval prior to distributing a product with the label change. In such a supplement, the applicant is required to present clearly the proposed change in the label and the information necessary to support the proposed change. The following list contains some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.
7. Change in container labels for licensed blood.

B. Changes under §601.12(f)(2) - Labeling changes requiring supplement submission - product with a labeling change may be distributed before FDA approval.

Under §601.12(f)(2), a supplement is required to be submitted for any change to a package insert, package label, or container label that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safety of the use of the product; or deletes false, misleading, or unsupported indications for use or claims for effectiveness. The applicant may

distribute product with a label bearing such a change at the time the supplement is submitted, although the supplement is still subject to approval by FDA. The following list includes some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Addition of an adverse event due to information reported to applicant or FDA.
2. Addition of a precaution arising out of a post-marketing study.
3. Clarification of the administration statement to ensure proper administration of the product.

C. Changes under §601.12(f)(3) - Labeling changes requiring submission in an annual report.

Under §601.12(f)(3), a package insert, package label, or container label with editorial or similar minor changes or with a change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form is required to be described in an annual report. Some examples that are currently considered by FDA to fall into this reporting category include:

1. Changes in the layout of the package or container label without a change in content of the labeling.
2. Editorial changes such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.

Guidance for Industry

Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Christopher Joneckis (CBER) 301-435-5681, Stephen Moore (CDER) 301-827-6430, or Dennis Bensley (CVM) 301-827-6956.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Veterinary Medicine
September 2003

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Comparability Protocols Protein Drug Products and Biological Products - - Chemistry, Manufacturing, and Controls Information

Additional copies of this guidance are available from:
Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
1401 Rockville Pike, Rockville, MD 20852-1448
Phone: 800-835-4709 or 301-827-1800
Internet: http://www.fda.gov/cber/guidelines.htm
or
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
5600 Fishers Lane, Rockville, MD 20857
Phone: 301-827-4573
Internet: http://www.fda.gov/cder/guidance/index.htm
or
Communications Staff, HFV-12
Center for Veterinary Medicine (CVM)
7519 Standish Place
Rockville, MD 20855
Phone: 301-827-3800
Internet at http://www.fda.gov/cvm/guidance/published.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Veterinary Medicine
September 2003

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]

Comparability Protocols- Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternate approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this document.

I. INTRODUCTION

This guidance provides recommendations to you, the applicant, on preparing and using comparability protocols for changes in chemistry, manufacturing, and controls (CMC) of products[2] in approved marketing applications. A comparability protocol is a comprehensive plan that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product, as they may relate to the safety or effectiveness of the product. FDA's review of the comparability protocol will include a determination of whether changes made in accordance with that protocol may be submitted under a reduced reporting category for the change because the use of the protocol reduces the potential risk of an adverse effect.

This guidance applies to comparability protocols that you would submit in biologics license applications (BLA), or supplements to BLA applications, for therapeutic recombinant DNA derived protein products, naturally derived protein products, plasma derivatives, vaccines, allergenics and therapeutic DNA plasmids. This guidance also applies to new drug applications (NDAs), abbreviated new drug applications (ANDAs),[3] new animal drug applications (NADAs), abbreviated new animal drug

[1] This guidance has been prepared by the Comparability Protocol Working Group, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Veterinary Medicine (CVM) at FDA.

[2] The general term *product* as used in this guidance means drug substance, drug product, and intermediate, or in-process material, as appropriate.

[3] Section 505 of the Federal Food, Drug, and Cosmetic Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an

applications (ANADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixture of small peptides).[4]

This guidance does not pertain to comparability protocols for human blood and blood components intended for transfusion and for further manufacture,[5] somatic cell therapy, or gene therapy vectors (except therapeutic DNA plasmids). This guidance also does not pertain to vaccines for veterinary use, which are regulated by United States Department of Agriculture.

FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

You are responsible for assessing, prior to distribution of a product, the effect of any postapproval CMC changes on the identity, strength, quality, purity, and potency of the product as they may relate to the safety or efficacy of the product). Such an assessment often includes data that demonstrate that the pre- and post-change products (i.e., the products manufactured prior to and subsequent to a manufacturing change) are comparable. You must report postapproval CMC changes to FDA, us, in one of the reporting categories described by FDA (section 506A(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 356a).[6] (See II.E for references). As part of its review and approval of a comparability protocol to evaluate the effects of a change, if supported by the submission, FDA may determine that a CMC change made under the comparability protocol will fall into a less restrictive reporting category. In many cases, using a comparability protocol will facilitate the subsequent implementation and reporting of CMC changes, which could result in moving a product into distribution sooner than if a protocol were not submitted.

---

application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)).

[4] When finalized, guidance on comparability protocols that can be submitted in NDAs, ANDAs, NADA, and ANADAs for many products outside the scope of this guidance will be provided in "Guidance For Industry: Comparability Protocols -Chemistry, Manufacturing, and Controls Documentation." FDA published a draft version of this guidance on February 25, 2003 (68 FR 8772).

[5] Guidance on comparability protocols for human blood and blood products can be found in "Guidance For Industry: Changes to an Approved Application: Biologics Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001."

[6] See also 21 CFR 601.12.

58
59 • Annual Report (AR)
60
61 This annual submission to the approved application reports changes that have minimal potential to
62 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
63 the safety or effectiveness of the product.
64
65 • Change-Being-Effected Supplement (CBE)
66
67 This submission to an approved application reports changes have moderate potential to adversely
68 affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety
69 or effectiveness of the product. A CBE supplement would be received by FDA before, or
70 concurrently with, distribution of the product made using the change. It is distinguishable from a
71 Change-Being-Effected-in-30-Days Supplement (discussed below) because FDA has determined
72 that, based on experience with a particular type of change, the supplement for such change is usually
73 complete and provides the proper information, and based on assurances that the proposed change
74 has been appropriately submitted, the product made using the change may be distributed
75 immediately upon receipt of the supplement by FDA.
76
77 • Change-Being-Effected-in-30-Days Supplement (CBE-30).
78
79 This submission to an approved application reports changes that have moderate potential to
80 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
81 the safety or effectiveness of the product. A CBE-30 supplement would be received by FDA at
82 least 30 days before you may distribute the product made using the change (21 CFR 601.12(c)(3)).
83
84 • Prior Approval Supplement (PAS)
85
86 This submission to an approved application reports changes that have a substantial potential to
87 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
88 the safety or effectiveness of the product. FDA would receive and approve a PAS before you may
89 distribute the product made using the change (21 CFR 601.12(b)).
90
91 This guidance describes the general principles and procedures associated with developing and
92 submitting a comparability protocol to us. This guidance also describes the basic elements of a
93 comparability protocol and specific issues to consider when developing comparability protocols for
94 changes in:
95

- the manufacturing process,
- analytical procedures,[7]
- manufacturing equipment,
- manufacturing facilities,
- container closure systems, and
- process analytical technology (PAT).

This guidance also discusses submitting comparability protocols in master files.

A. What is a Comparability Protocol?

A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes on the identity, strength, quality, purity, and potency of a specific drug product as they may relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be met to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is not required to make a CMC change.

B. What is the Benefit of Using a Comparability Protocol?

At the same time we approve a comparability protocol, we can designate,[8] if appropriate, a reduced reporting category for future reporting of CMC changes covered by the approved comparability protocol (See section III.A). Furthermore, because a detailed plan will be provided in the comparability protocol, we are less likely to request additional information to support changes made under the protocol (See section IV.D for a potential exception). The use of a comparability protocol could allow an applicant to implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol.

C. When and Why Were Comparability Protocols Created?

For many years, applicants have used protocols to implement certain types of CMC changes, such as to extend an expiration dating period or to demonstrate the interchangeability of certain plastic containers. More recently, there have been many improvements in the techniques for characterizing products, production processes, process controls, and release testing. Because of these improvements and

[7] The term *analytical procedure*, as used in this guidance, includes, biochemical, chemical, physicochemical, immunochemical, microbiological, and biological test procedures.

[8] The term *designate*, in this context, refers to the reporting category agreed to by the applicant and FDA during the review of the submission containing the comparability protocol. See Section V.A.6.

because we are able to better assess the potential effect of CMC changes on a product, protocols are now being used with other types of CMC changes (e.g., manufacturing process, analytical procedure changes). This expanded use of comparability protocols has been recognized in FDA regulations,[9] and we have received a number of requests for guidance from applicants interested in using comparability protocols for these other types of changes. The use of comparability protocols for expanded types of CMC changes has allowed some applicants to implement CMC changes sooner.

D. Why is A Guidance on Comparability Protocols Being Provided?

We have received a number of requests for guidance from applicants interested in using comparability protocols for CMC changes. Our experience in reviewing comparability protocols for a variety of CMC changes for biologics, including specified products and protein drug products, has been incorporated into this guidance.

E. Where Can More Information on Postapproval Changes and Assessment of Comparability Be Found?

This guidance is not intended to supersede other FDA guidance documents, but rather to supplement them with information on using comparability protocols to implement postapproval CMC changes. We recommend that you consult all relevant guidances[10] for information relating to postapproval changes. The following guidances provide relevant information on: (1) assessing the effect of CMC changes on product attributes, (2) providing documentation to support postapproval change, and (3) the recommended reporting categories.

- *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products Including Therapeutic Biotechnology-derived Products, (April 1996)*
- *Guidance For Industry: Changes to an Approved Application For Specified Biotechnology and Specified Synthetic Biological Products (July 1997)*
- *Guidance For Industry: Changes to an Approved Application For Biological Products (May 1996)*
- *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an Approved NDA or ANDA*[11] (November 1997)
- *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an Approved NADA or ANADA* (draft) [10, 12] (June 1999)

[9] See, for example, 21 CFR 601.12(e). These regulations provided for the use of a pre-specified protocol, or a comparability protocol, that describes how to assess the effects of specific manufacturing changes.

[10] Relevant guidance documents can be found on the internet at http://www.fda.gov/cder/guidance/index.htm, http://www.fda.gov/cber/guidelines.htm, or http://www.fda.gov/cvm/guidance/published.htm

[11] Guidance for naturally derived protein drug products

[12] This draft guidance is listed for completeness but is not intended for implementation until it has been finalized.

III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL

A. How Does a Comparability Protocol Affect the Reporting of CMC Changes?

A comparability protocol *prospectively* specifies the planned CMC change, the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be met to assess the effect of CMC changes. A well-planned protocol provides sufficient information for us to determine whether the potential for an adverse effect on the product can be adequately evaluated. When we review a comparability protocol, we will determine if a specified change can be reported in a reporting category lower than the category for the same change implemented *without* an approved comparability protocol. Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30, CBE to AR). In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).

B. When Might a Comparability Protocol Be Useful for a CMC Change?

A comparability protocol could be useful for a variety of CMC changes, but there are some exceptions (See Section III.C). In addition, a comparability protocol can describe a single CMC change or multiple related changes, and can be particularly useful for changes of a repetitive nature. Because biologics and protein drug products are complex and heterogeneous, knowledge of how product attributes affect the safety and efficacy of the product is crucial in designing most comparability protocols. It is also important that you have sufficient manufacturing and analytical experience to specify in advance the tests, studies, analytical procedures, and acceptance criteria appropriate to assess the impact of the change on the product. We recommend that you include information from developmental and investigational studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, and stability data with the particular product and process, and in some cases manufacturing information with similar products or processes (e.g., for some monoclonal antibody products). However, we also recognize that some CMC changes (e.g., some packaging changes) would require less supportive information because they are less dependent on manufacturing experience. We recommend that you submit comparability protocols only for CMC changes that you intend to implement.

We recommend that you consider product-specific and process-specific attributes when determining whether to develop a comparability protocol. Attributes can include, but are not limited to, the following:

- Complexity of the product structure,
- Ability to characterize the physicochemical, biochemical, immunological microbiological, and biological properties of the product,