Guidance for Industry

Changes to an Approved Application: Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 1997

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I. INTRODUCTION

Frequently, a licensed applicant determines that it is appropriate to make a change in the product, labeling, production process, quality controls, equipment, facilities, or responsible personnel established in the approved license application(s). Section 601.12 of Title 21 of the Code of Federal Regulations (21 CFR 601.12) prescribes the requirements for reporting such changes for licensed biological products to FDA.

Under §601.12, a change to a product, production process, quality controls, equipment, facilities, or responsible personnel is required to be reported to FDA in 1) a supplement requiring approval prior to distribution, 2) a supplement at least 30 days prior to distribution of the product made using the change, or 3) an annual report, depending on its potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as they may relate to the safety or effectiveness of the product. Before distributing a product made using a change, applicants are required to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product.

The three reporting categories for changes to an approved application are defined in § 601.12: 1) those changes 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

[1] This guidance document represents FDA's current thinking on changes to an approved application for all licensed biological products, except the specified biotechnology and specified synthetic biological products listed in § 601.2(c). 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. Written requests for single copies of this document may be submitted to the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The document may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the World Wide Web (WWW) or bounce-back e-mail. For WWW access, connect to CBER at "http://www.fda.gov/cber." To receive the document by bounce-back e-mail, send a message to "changes@a1.cber.fda.gov."

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.