

# Comparability Protocol Resource

**Purpose:** To provide a resource for developing and submitting a comparability protocol to FDA in support of a Biologics License Application (BLA) or Supplement.

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## Introduction

A Comparability Protocol (CP) is a highly specific, well-defined plan for the future implementation of a Chemistry, Manufacturing and Controls (CMC) change. The purpose of a CP is to allow for a more expedient distribution of product by permitting you to submit a protocol for a change, which if approved, may justify a reduced reporting category for the particular change at the time the change is implemented. A new CP, or a change to an existing one, requires approval prior to implementation because it may result in a decreased reporting category for the changes covered in the CP. 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). The reporting category will be established by the FDA at the time that the CP is approved.

A proposed CP can be submitted in one of the following three ways:

1. As a prior approval supplement that consists only of the proposed comparability protocol. You may want the FDA to review and approve the protocol and determine the reporting category for changes, evaluated under the protocol, prior to generating data specified in the protocol.
2. As a prior approval supplement that includes the proposed comparability protocol, study results, and any other pertinent information as specified in the proposed comparability protocol. Note that the comparability data submitted would be evaluated as part of the prior approval supplement. The product already manufactured with the change can be distributed only after approval of the supplement.
3. As part of an original market application (i.e., PAS). You may want the comparability protocol reviewed and approved and the reporting category determined, prior to generating data specified in the protocol.

## Definitions and Abbreviations

The table below lists the abbreviations that are used throughout this document.

Abbreviation/Term	Definition
AR	Annual Report
BLA	Biologics License Application
CBE30	Changes Being Effected in 30 Days
CBER	Center for Biologics Evaluation and Research
CMC	Chemistry, Manufacturing and Controls
CoI	Circular of Information
CP	Comparability Protocol
FDA	Food and Drug Administration
Form FDA 2567	Transmittal of Labels and Circulars
Form FDA 356h	Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use
Form FDA 3674	Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))
PAS	Prior Approval Supplement
QC	Quality Control
SOP	Standard Operating Procedure
STN	Submission Tracking Number

## Applicability of a Comparability Protocol

Prior to developing a CP, an assessment should be conducted to determine if a CP is appropriate for the change. Generally, the change should be a discrete, specific manufacturing change in a facility, equipment, or process. There should be sufficient manufacturing experience and acceptance criteria available to demonstrate that the change does not have an adverse effect on the safety or effectiveness of the product.

A CP should only be considered if:

1. The product manufactured using the change will meet approved product standards.
2. The manufacturing process has been validated and all equipment qualified.
3. Appropriate validated assays are available to evaluate the effect of the change on the product.

Examples of changes for which a CP might be useful are:

1. Acquisition of facilities operating under one manufacturer's license by another licensee.
2. Single change in the manufacture of a product that will be implemented in multiple facilities under a single license (e.g., plateletpheresis).
3. Change to use a cleared apheresis device for the collection of products approved for this device (e.g., use of Fenwal Amicus to also collect Platelets, Pheresis; Platelets, Pheresis, Leukocytes Reduced; and Fresh Frozen Plasma, concurrently with plateletpheresis).

However, the use of a CP is not appropriate for all manufacturing changes. Certain changes may be too critical, complex, or of such a magnitude that a CP cannot be designed to adequately evaluate the effect of the change on the safety and effectiveness of the product. In such cases, a PAS would need to be submitted to implement the change. Also, changes already reported as CBE or in the annual report would have little benefit as a CP.

In general, the use of a CP is not appropriate for:

1. Broad ranging plans, covering any conceivable change in the manufacturing process.
2. A change with the potential to adversely affect the product.
3. A change where pre-specified acceptance criteria are not available to determine the effect of the change on the product.
4. A change resulting in a newly characterized product that is not currently licensed.
5. The use of a new manufacturing facility for which a pre-license inspection would normally be conducted.
6. A change in a facility, equipment or process for which a pre-approval inspection would normally be conducted.

## Components of a Comparability Protocol Submission

The initial submission of a CP is always submitted as part of a prior approval supplement (PAS). As with any PAS submission, the FDA requires the following information:

1. Cover Letter.
2. Form FDA 356h, *Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use*.
3. Detailed description of the proposed change.
4. List of the products involved.
5. Manufacturing sites or areas affected.
6. 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 as related to safety and effectiveness.
7. Data from all studies performed.
8. Validation protocols and data.
9. Relevant SOPs (changes should be highlighted).
10. Relevant labels.
11. Form FDA 2567, *Transmittal of Labels and Circular*.

In addition to the information required for all PAS submissions, some or all of the following should be included in the CP submission:

1. Description of the planned manufacturing change.
2. Implementation plan.
3. Specific tests and validation protocols (include the rationale for selecting the specific tests and protocols).
4. Criteria for acceptance of product prepared under changed conditions.
5. Description of actions taken if the acceptable results are not achieved.
6. Supportive data obtained from selected testing.
7. Training program.
8. Quality assurance program, including quality control testing plan.
9. Product submission sampling plan.
10. Proposed change in reporting category.

The following checklists are one suggestion of how to compile a CP submission which would address the required FDA elements.

## Cover Letter

FDA continues to encourage applicants to use a cover letter to introduce and summarize an application. It is recommended that the following topics be included in the cover letter:

Statement/purpose of submission – included in first paragraph.	
Full facility name, FDA registration and license numbers.	
Collection facility name, FDA registration and license numbers.	
Date of most recent FDA inspection (optional).	
Product(s) requested for licensure.	
Manufacturing site(s) and their CFN/FEI (includes off-site donor or QC testing).	
Statement requesting a new reporting category.	
Description of the manufacturing change.	
Description of validation, QC testing, and training, including a statement indicating that each site will perform the same.	
List of all attachments included in the submission.	
Contact information for questions, concerns or requests for additional information.	
Statement clarifying that this is the facility’s comparability protocol for use with future submissions.	

## Forms

<p>Form FDA 365h -- it is the “cover sheet” that allows proper identification, routing and filing of the attached information.</p> <ul style="list-style-type: none"> <li>▪ Product Description – enter established and chemical name; refer to “CoI” for indications; all else in this section is “N/A.</li> <li>▪ Application Description – check the “BLA” and “CMC” boxes; check “PAS” box. Briefly describe the reason for the submission.</li> <li>▪ Establishment Information – indicate “see cover letter.”</li> <li>▪ Cross-references – list any applicable previously approved STNs with approval dates or applicable CP with approval date.</li> <li>▪ Page 2 of the 356h – check boxes 4, 4A, and 20.</li> </ul>	
Form FDA 2567 should be submitted with relevant labels.	
Form FDA 3674 should be submitted with application, if applicable.	

Note: To obtain the FDA forms, go to <http://www.fda.gov/opacom/morechoices/fdaforms/>. Instructions for completing Form FDA 356h are found in “Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the form FDA 356h ‘Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use.’” The guidance can be obtained at <http://www.fda.gov/cber/gdlns/cmcblood.pdf>. Instructions for completing Form FDA 3674 are found at <http://www.fda.gov/cder/forms/1571-1572-help.html#form3674>.

## Quality Assurance Plan

The quality assurance plan should incorporate quality assurance principles for the specific process. It is recommended that the following topics be included:

Description of the responsibilities for the department(s) involved.	
SOPs describing the specific process and quality control procedures.	
Brief description of training procedures.	
Training documents and documentation of the qualification of trainers (e.g., trained by company).	
Description of the competency evaluation process.	

## Validation Plan

The validation plan should ensure that the process will consistently perform as expected. It is recommended that the following topics be included:

Validation objective.	
Installation, Operational and Process or Product Performance Qualifications with a description of the specific tests and the rationale for selecting those tests.	
Acceptance criteria.	
Validation summary/outcome.	

## Implementation Plan

The implementation plan should describe how the process will be executed at each site. It is recommended that the following topics be included:

Time frame for implementation at each site.	
Length of time for training.	
Sampling plan for quality control testing, validation testing and samples sent to the FDA for evaluation.	
Description of the ongoing process of monthly quality control testing.	
Definition of acceptance criteria of the product with a description of actions to be taken if the results are not acceptable.	
An evaluation of the process and effectiveness of the plan through periodic audits.	

## **Reporting of the Manufacturing Change(s) Implemented Using an Approved Comparability Protocol**

The actual change implemented should be submitted using the approved CP via the reporting category that the FDA specified in the approval letter. In subsequent submissions, describe the change, refer to the approved CP, and include all the data committed to be collected under the CP.

The CP may contain supportive data and a request to distribute product made with the specified manufacturing change or may only contain the implementation procedures described in section 'Components of a Comparability Protocol Submission' above with a request to review and approve the CP before the supportive data are generated. If the CP is accompanied by supporting data and is approved, the product made using the change described in the CP can be distributed. If the CP is approved prior to the generation of data supporting the change, the supportive data should be submitted in the reduced reporting category specified in the approval letter.

### **References**

1. Code of Federal Regulations, Title 21 part 601.12
2. Guidance for Industry, Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, July 2001.
3. Draft Guidance for Industry, Comparability Protocols – Chemistry, Manufacturing, and Controls Information, February 2003.