

Guidance for Industry

Format and Content for the CMC Section of an Annual Report

Center for Drug Evaluation and Research (CDER)
September 1994

GUIDANCE FOR INDUSTRY¹

FORMAT AND CONTENT

FOR THE CMC SECTION OF AN ANNUAL REPORT

I. PURPOSE

To describe the information requested by the Center for Drug Evaluation and Research (CDER) in an Annual Report to a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Abbreviated Antibiotic Application (AADA) submitted pursuant to 21 CFR 314.81(b)(2).

The primary objective is to ensure consistency and completeness of information in the Annual Reports submitted by the pharmaceutical industry and to standardize the general format.

II. BACKGROUND

The FDA regulations for the submission of Annual Reports are described in 21 CFR 314.70(d) and 21 CFR 314.81(b)(2). In the past, the reports submitted under these regulations have exhibited wide variability from firm to firm, and at times the information submitted has been inconclusive or insufficient.

This guidance addresses information that should be included in an Annual Report. It may also be helpful to consult other Center guidances for information on the depth of technical information requested. For example, CDER's *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* provides information on the design of stability protocols, the amount of stability data that should be provided to support specific changes to the application (e.g., packaging changes submitted under

¹This guidance has been prepared under the auspices of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the submission of chemistry, manufacturing, and controls information in an annual report. For additional copies of this guidance, contact the Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012). Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using FTP, Gopher or the World Wide Web (WWW). For FTP, connect to the CDER anonymous FTP server at CDVS2.CDER.FDA.GOV and change to the "guidance" directory. For Gopher, connect to the CDER Gopher server at GOPHER.CDER.FDA.GOV and select the "Industry Guidance" menu option. For WWW, connect to the FDA Home Page at WWW.FDA.GOV/CDER.

314.70(d)(6)), and guidance on the extension of the expiration dating period. Complete information submitted in an easy to follow format will assist the reviewer in conducting an efficient review.

CDER encourages the applicant to contact the appropriate office or division if there is uncertainty whether the information should be submitted in an annual report or as a supplemental change to the approved application.

III. POLICY

The NDA/ANDA/AADA holder should follow the procedure outlined in Form FDA 2252 when filing an Annual Report. Annual Reports should be filed for all approved NDA's, ANDA's and AADA's (including those for bulk antibiotic drugs), regardless of their activity status. For NDA's filed with the Offices of Drug Evaluation I or II, applicants should submit sufficient copies of the Annual Report for the jacket of each affected discipline so as to assure concurrent review.

The applicant should follow the format described below and include all information when preparing an Annual Report. If no changes were made in a particular section during the reporting period, the applicant should state "No changes were made during the reporting period." Please note that even though the format described below may not be entirely complete, the firm remains responsible for complying with all requirements under current regulations.

IV. FORMAT

SECTION I. SUMMARY OF NEW INFORMATION

The firm should include a brief summary of all changes made to the application during the reporting period, including changes made in accordance with approved supplements under 21 CFR 314.70(b) and special supplements under 21 CFR 314.70(c). All changes should be highlighted or annotated within the Annual Report and should be included in the list of approved chemistry, manufacturing and control information described in Section IV of this document.

SECTION II. DISTRIBUTION DATA [21 CFR 314.81(b)(2)(ii)]

The firm should provide:

- A. The quantity distributed of each currently approved strength by package size (e.g. number of 30's, 100's for drug products or kg for bulk antibiotic drugs), or

- B. The statement "None distributed" along with the corresponding approved package size(s) if there is no distribution for that package size.
- C. Quantities distributed for domestic use and quantities distributed for foreign use.
- D. For bulk antibiotic drug AADA's, a current list of all persons authorized to reference the application and any person whose authorization has been withdrawn.

Distribution information should be distributor-specific.

SECTION III. LABELING [21 CFR 314.70(d), 21 CFR 314.81(b)(2)]

Generally, any labeling change submitted in an Annual Report should include supportive documentation (e.g. submission of a statement of the currently approved composition to support upgrading insert labeling to include previously unlisted inactive ingredients).

Information submitted under 21 CFR 314.81(b)(2)(iii), should include the following:

- A. All currently used labeling, including a representative sample of package labels. This should include all package inserts and examples of the immediate container labels. It may be useful to include labels of distributors. Samples of all labeling which has undergone a change during the reporting period, including immediate container labels, carton labeling, and insert labeling, should be provided in the Annual Report.
- B. A summary of any changes made in the labels/labeling since the last Annual Report, listed chronologically by implementation date.

SECTION IV. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES

CDER requests that a current list of approved chemistry, manufacturing and control information be provided yearly in the Annual Report to better document the changes occurring in applications. This index is not for review purposes, but will serve as a reviewer aid. The list should include all information shown in Attachment 1 and the use of the format in the attachment is encouraged. The information should include the type and date of each change to each component, the type of submission used to report the change (Original, Supplemental or Annual Report), and the date the change was reported and approved, if it was.

Regulatory specifications and analytical methods for the drug substance and drug product should be listed individually as illustrated below:

III. SPECIFICATIONS AND METHODS FOR THE DRUG SUBSTANCE

<u>Test</u>	<u>Specification</u>	<u>Method (#, Reference)</u>
Description	Clear, Colorless Liquid	Visual (CZT2001, Original[2-3-86])
Assay	98 - 102%	HPLC (CZT2019, S-003[4-11-81])
	*	*

Examples of chemistry, manufacturing and controls changes that should be reported include but should not be limited to the following information:

A. Compendial Changes [21 CFR 314.70(d)(1)]

Changes made to comply with changes in an official compendium should include:

- (1) Full description of changes in test methods and limits.
- (2) Data demonstrating the suitability of the compendial change for the drug product.

B. Formulation [21 CFR 314.70(d)(4)]

Deletion of an ingredient intended only to affect the color of the drug product should be reported and include:

- (1) A comparative component and composition statement, with all changes highlighted or annotated.
- (2) A statement of the current component and composition in subsequent Annual Reports, including reference to the change (i.e. date, Annual Report Number, or Supplement Number).

- (3) Revised labeling as required by 21 CFR 314.70(d)(2) reflecting the change in formulation.

C. Expiration Period [21 CFR 314.70(d)(5)]

Extension of the expiration dating period should be accompanied by full shelf-life stability data for the proposed expiry dating on a minimum of three production lots and a justification for the change in the expiration date. The data should be obtained using the stability protocol approved in your application.

D. Container/Closure [21 CFR 314.70(d)(6)]

Changes within the approved container and closure system for a solid oral dosage form may be included in the annual report (e.g., one HDPE to another HDPE). The description of this change should be accompanied by the following information:

- (1) Components and manufacturer. Letters of authorization allowing reference to other documents (e.g., DMFs) should be included if appropriate.
- (2) Testing results that demonstrate the equivalency of the changed container and closure system to the original system in accordance with compendial requirements or a protocol approved in the application.
- (3) A Statement of Commitment to place the drug product using the changed container and closure system in stability studies using the approved stability protocol.

E. Test Methods [21 CFR 314.70(d)(7)]

The applicant should submit the following information for the addition or deletion of an alternate method:

- (1) A brief statement explaining the reason for the deletion.
- (2) Data demonstrating the suitability and validation of the new alternate method compared to the reference method. The data should demonstrate the alternate method is equivalent or superior to the current regulatory method.

F. Container/Closure [21 CFR 314.70(d)(8)]

A change in the size of a container for a solid oral dosage form, without a change from one container and closure system to another, should be consistent with the Center for Drug Evaluation and Research Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.

G. Status Report [21 CFR 314.81(b)(2)(vii)]

CDER strongly recommends that the stability report format for the Annual Report include the following information along with the data accumulated from your ongoing stability studies:

STABILITY REPORT

NAME/STRENGTH:	BATCH #/STUDY #:	BATCH/SIZE:
DATE MANUFACTURED:	MANUFACTURING SITE:	CONTAINER SIZE/SUPPLIER:
DATE PACKAGED:	PACKAGER/SITE:	CONTAINER RESIN:
DATE STUDY STARTED:	PURPOSE OF STUDY:	CLOSURE/SUPPLIER:
DATE OF EXPIRY:	STORAGE CONDITIONS (INCLUDE ORIENTATION):	SEAL/SUPPLIER:
	DRUG SUBSTANCE	FILLER:
	MANUFACTURER/SITE/LOT#:	

ATTRIBUTES	METHODS SOP#	SPECIFICATIONS (LOW/HIGH)	TIME (MONTHS)						
			0	3	6	9	12	18	...
APPEARANCE									
ASSAY									
PURITY DEG PROD A DEG PROD B DEG PROD C									
pH									
ETC...									
ACTUAL TEST DATES	xxxxxxxxx	xxxxxxxxxxxxxxxxx							

The actual date that the sample(s) were tested should be included in the bottom row of the table.

If there was no product distribution during the reporting period, the firm should state the status of the ongoing stability program as stated in the approved protocol.

Approved by CMC CC:

Charles Kumkumian, Ph.D.

Roger L. Williams, M.D.

ATTACHMENT 1

NDA/ANDA/AADA #####
 INDEX OF APPROVED CHEMISTRY, MANUFACTURING AND CONTROLS
 INFORMATION

		SUBMISSION		APPROVAL
		TYPE	DATE	DATE
I.	DRUG SUBSTANCE			
	A. Manufacturer(s)	_____	_____	_____
	B. Method(s) of Manufacture	_____	_____	_____
	C. Container and Closure	_____	_____	_____
	D. Stability Protocol	_____	_____	_____
	E. Specifications and Analytical Methods *			
II.	DRUG PRODUCT			
	A. Composition	_____	_____	_____
	B. Manufacturer(s)	_____	_____	_____
	C. Method(s) of Manufacture and Packaging	_____	_____	_____
	D. Specifications and Analytical Methods *			
	E. Container(s) and Closure(s)	_____	_____	_____
	F. Expiration Dating Period _____ Months	_____	_____	_____
	G. Stability Protocol	_____	_____	_____

*Please attach a complete listing of the Specifications and Analytical Methods for the drug substance and drug product in the format provided.

III. SPECIFICATIONS AND METHODS FOR THE DRUG SUBSTANCE

<u>TEST</u>	<u>SPECIFICATION</u>	<u>METHOD (#, Reference)</u>
-------------	----------------------	-------------------------------

IV. RELEASE SPECIFICATIONS AND METHODS FOR THE DRUG PRODUCT

<u>TEST</u>	<u>SPECIFICATION</u>	<u>METHOD (#, Reference)</u>
-------------	----------------------	-------------------------------