# PHARMACEUTICAL SCIENCE

## Chemistry Reviews of DMFs for Drug Substances/Intermediates (DSI)

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**PURPOSE** This MAPP establishes Center policy for reviewing information filed in type II drug master files (DMFs) in support of drug product applications. This policy applies to DMFs for drug substances and key, pivotal, or final intermediates that require review (i.e., drug substance/intermediate drug master files — DSI-DMFs). The policies established by this document are intended to standardize Center procedures for reviewing new and previously reviewed information contained in this class of DMFs.

**BACKGROUND**

- A DMF is a submission to the Food and Drug Administration intended to provide confidential information in support of an investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), DMF, or export application, amendment, or supplement to any of these. The Agency reviews the information only in the context of a

specific drug product application, and the FDA neither approves nor disapproves submissions to drug master files. Some DMFs are referenced in a number of applications and may have been reviewed, in whole or in part, during reviews of those applications. Different sections of the DMF may be judged to be "Adequate" or "Inadequate."

- An applicant must provide the following information regarding a drug substance ((21 CFR 314.50(d)(1)(I)):

  A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form.

  A DMF for the manufacture of a drug substance allows the applicant to incorporate this information by reference. Therefore the DMF holder must provide this information in the DMF. Information provided in a DMF is reviewed in conjunction with the review of the application.

- DMFs containing chemistry manufacturing and controls (CMC) information for an intermediate are also reviewed in support of an application. See the guidance for industry entitled *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (2/1/87) for the criteria for classifying a material as an intermediate.

## REFERENCES

- 21 CFR 314.420, Drug master files
- Guidance for Industry, *Drug Master Files* (9/1/89)
- DMF Review Cover Form (MAPP 5015.3)
- Guidance for industry, *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (DSG) (2/1/87)

## DEFINITIONS

- **Applicant.** The company or entity that submits an application. The applicant is also sometimes called a sponsor, although this term should be reserved for a company or entity that submits an IND.

- **Application.** An IND, NDA, ANDA, DMF or export application that references the DMF.

- **DMF.** A submission of information to the Food and Drug Administration intended to provide confidential information in support of an application, amendment, or supplement to any of these.

- **Drug Substance.** As defined in 21 CFR 314.3(b), a drug substance is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredients.

- **DSI-DMF.** A DMF containing information about the preparation of an active drug substance or an intermediate used in the preparation of an active drug substance (see DSG).

- **Holder.** The company or entity that submits a DMF.

- **Letter of Authorization (LOA).** A letter from the holder that authorizes an applicant to incorporate by reference all or part of the contents of the DMF in support of an application and authorizes FDA to review this information.

- **Specification.** A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. (From *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* International Conference on Harmonisation (ICH), March 1997).

## POLICY

### I. Written Review

There are four types of written reviews: initial review, review of amendments in response to an Agency letter, additional review, and re-review. If any part of the submission is found to be inadequate, the holder is informed of the specific deficiencies, and the applicant is notified that deficiencies exist in the DMF. (See Attachments A and B.)

- **Initial review.** The first review of a DMF should encompass all information dealing with the referenced item or topic in the original DMF submission and any amendments or annual updates, unless it is clearly stated that some of the information has been superseded.

- **Review of amendments in response to Agency letter.** An amendment in response to an Agency letter is reviewed when:

  1. The applicant has amended the application supported by the DMF to inform the Agency that the DMF deficiencies have been addressed; or

  2. A second application references the DMF before the first application has been amended. The reviewer of the second application should notify the original reviewer of his or her intent to review the DMF amendment.

- **Additional reviews.** These reviews, written when additional information in the DMF is referenced by an application, cover the following submissions:

  1. Information previously submitted, but not reviewed.

  Certain attributes of the drug product (see list below) may require the use of a grade of drug substance (e.g., micronized) that was not previously reviewed. If the previous review of the DMF did not address this specific requirement for the drug substance, a review of the manufacturing procedures (e.g., milling) and controls of the drug substance in the DMF may be necessary. The reviewer should provide a basis for the review in the Comments section of the DMF Cover Form. However, prior authorization is not required.

  Drug Product Attributes:

  a. Dosage form

  Example: The applicant may require a certain particle size distribution for the drug substance to control the manufacture of a metered dose

inhaler drug product.

b. Route of administration

Example: If a drug product available for oral use is then submitted as an ophthalmic product, additional controls for the drug substance may be required.

c. Manufacturing process

Example: A different manufacturing procedure for a tablet is used (e.g. direct compression rather than wet granulation). The DMF may have to be reviewed for particle size distribution of the drug substance since this characteristic may be critical to the direct compression process.

d. Other

Situations may arise (dosing and/or route of administration) in which there may be a concern about acceptable levels of impurities. In this case, an additional review of the manufacturing process and the specifications may be necessary.

2. Spontaneous amendments

These are amendments containing new information that is not in response to an Agency letter. Examples include

a. New or revised impurity specifications
b. New synthetic procedures
c. Addition of a new specification (e.g., particle size)
d. Response to a change in compendial requirements or CDER policy.

- **Re-review.** A re-review (i.e., review of previously reviewed information) may be conducted under the following circumstances, regardless of whether the previously reviewed information was found to be adequate or inadequate.

1. Limited Scope - The prior review was limited in scope (e.g., as part of a safety review of an IND or for determining the fileabillity of an application).

2. Old review - If a DMF review is more than five years old, the DMF may

be re-reviewed.

3. Other - If a reviewer believes that a re-review should be conducted, documentation of the reason for the re-review should be submitted to the reviewer's team leader and to the DMF file. If the team leader concurs in the decision, then re-review may proceed with no additional documentation. However, the team leader should notify the team leader of the team in which the earlier review was performed. If the team leader does not concur with the reviewer's decision to perform a re-review, the team leader must submit a memorandum to the file stating the reasons for nonconcurrence and the reviewer may not proceed with the review.

Examples:

a. The previous review was done before a standard review format was available and the review does not document that all salient points were considered.

b. Safety concerns have arisen as a result of adverse drug reports.

## II. No Written Review Required

A written review of a DMF is not required under the following circumstances:

- Sufficient information is contained in the application itself.
- New administrative information is submitted (e.g., letters of authorization, annual updates with no CMC changes).
- The reviewer accesses a DMF only to obtain administrative information (e.g., manufacturing address).
- There is a previous review of the referenced information in the DMF, except as listed under "Re-review" above.

## RESPONSIBILITIES

### Review chemist

- Determines whether a review of a DMF is necessary and conducts the review.

**Chemistry team leader**

- Signs off on the DMF review
- If there is concurrence in a reviewer's request to re-review a previously reviewed DMF:
  ◆ Signs off on the reviewer's memo requesting the re-review.
  ◆ Notifies the team leader of the team in which the earlier review was performed.
- If there is nonconcurrence in a reviewer's request to re-review a previously reviewed DMF:
  Issues memo of non-concurrence in reviewer's request to re-review a previously reviewed DMF.

## PROCEDURES

### Authorization

The reviewer should determine that a letter of authorization (LOA) has been provided and that the relationship between the applicant and holder is clearly defined.

### Written review

If a written review of information in the DMF is required under the above policies, a review of the DMF should be prepared following the review notes format and accompanying instructions (Attachment A & B). The DMF cover form should be completed (MAPP 5015.3).

### Review status

The review status of DMFs referenced in an application should be documented in the chemistry review of that application. If a DMF is not reviewed because there is a previous review of the DMF information, the date and status of the previous review should be included.

### Communications with holder

If there are deficiencies in the DMF, these should be communicated to the holder in a

letter. If the DMF is not current, the holder should be asked to update the DMF. A DMF is current when an annual report (or amendment) has been filed in at least two of the past three years. Such an annual report or amendment may contain new information and a declaration stating that no changes have taken place.

**Communications with the applicant**

If a letter is sent to the holder, the applicant is informed that the DMF is deficient and that approval of the application is contingent on the correction of these deficiencies. However, no specific DMF deficiencies are revealed to the applicant.

## FORMAT

- Cover form (see MAPP 5015.3)
- Review notes format (Attachment A)

## AUTHORITY

This MAPP was prepared by the DMF Technical Committee under the authority of the Chemistry Manufacturing and Controls Coordinating Committee.

## EFFECTIVE DATE

This MAPP is effective upon date of publication.

**Attachment A**

## Review Notes Template

**I. DESCRIPTION and CHARACTERIZATION**
- A. Description and Physico-chemical Characteristics
- B. Characterization/Proof of Structure

**II. MANUFACTURER/TESTING FACILITIES**

**III. SYNTHESIS /METHOD OF MANUFACTURE**
- A. Starting Materials - Specifications
- B. Solvents, Reagents, etc.
- C. Flow Chart
- D. Detailed Description

**IV. PROCESS CONTROLS**
- A. In-Process Tests
- B. Specifications for Intermediates
- C. Reprocessing

**V. REFERENCE STANDARDS**

**VI. SPECIFICATIONS**
- A. Description
- B. Impurities
- C. Microbiology

**VII. CONTAINER/CLOSURE SYSTEM**

**VIII. STABILITY**

**IX. LABELING**

**X. COMMENTS AND LIST OF DEFICIENCIES**

**Attachment B**

## Instructions for Use of Review Notes Template for Drug Substance/Intermediate (DSI)-DMF Chemistry Reviews

## GENERAL COMMENTS

The review of a DMF should provide:

1. An administrative record of review;
2. A critical evaluation of the adequacy of the DMF to support a particular submission (e.g., NDA, ANDA, IND);
3. A guide for other reviewers; and
4. A technical information source for other parts of the Agency.

The review should ***not*** be a condensation of the DMF nor a repository for large amounts of data/information.

At the time of the writing of this MAPP, all DMF reviews are scanned into the Excalibur system. Because of this it is recommended that a font of at least 12 points in height be used and that a white or light-colored paper be used. In the near future, it is expected that DMF reviews will be filed electronically. This will permit retrieval of a review for use in preparing subsequent reviews.

The information submitted in a Type II DMF for drug substances/intermediates (DSI) should follow the DSG.

Intermediates whose synthesis and testing should be described, as specified in the DSG, should be reviewed using this review guidance.

The DMF should be reviewed according to the attached format. Guidance on what should be included **in the review** is described in the appropriate section. Each section (or subsection) of the review should contain the following elements, where applicable:

> **Data:** The amount of data included in the review should be sufficient to evaluate the section. Reproduction (whether by photocopying or by scanning) of the DMF information should be kept to a minimum. Where possible, information should be scanned in rather than photocopied so that the review will be complete in its electronic form. Analytical methods should be summarized rather than copied in full.

**Attachment B**

**Evaluation:** Each section should receive an evaluation; this may be brief if the information submitted is acceptable. If an item is not applicable or an essential item is omitted, this should be noted. Deficiencies, if any, should be identified and discussed.

**Conclusion:** The status [Adequate, Inadequate] of each section should be clearly indicated. Deficiencies in each section or subsection should be marked (e.g., with the word "Deficiencies" either in ***bold type*** or underlined). These deficiencies should be directly copied to the ***Comments and List of Deficiencies*** (Section X) at the end of the review.

After the initial review identifying deficiencies, there may be a series of reviews dealing with amendments submitted to correct the deficiencies. These subsequent reviews should follow the same format but should not repeat information previously captured in the original review. Each section with a deficiency should be reviewed for that particular issue. If a section was found to have no deficiencies in an earlier review, that should be noted with the date and review number of the earlier review, if available.

***Reminder: The following items are guidance about what should be included in the review and not what should have been submitted in the DMF.***

The general format with specific guidance on each section is outlined below:

## I. DESCRIPTION and CHARACTERIZATION

A. Description and Physico-Chemical Characteristics

The following are listed in the DMF cover form and need not be repeated:

USAN
CAS Name and CAS #
Molecular Weight
Chemical Formula
Structural Formula

Include the following elements in the review:

For USP items: Parameters not listed in the monograph (e.g., polymorphic form, stereochemistry, particle size.)

**Attachment B**

For Non-USP items:

- Appearance
- Solubility (limit data to aqueous solubility, pH effect, and at most one or two organic solvents)
- Partition coefficient (octanol/water)
- $pK_a$ (where applicable)
- Polymorphic form (where applicable)
- Particle size and/or surface area (where applicable)
- Melting point, specific rotation, etc.(where applicable)
- Miscellaneous (other important descriptive parameters)
- Stereochemistry (where applicable)

B. Characterization/Proof of Structure

Include the following elements in the review:

For USP items: Information necessary to establish identity.

For non-USP items:

- Preparation and purity of the material used for the characterization/proof of structure. Reference may be made to the preparation of the Reference Standard as noted in Section V.

- A summary of the evidence for proof of structure. Pages should be noted where the spectra and details can be found, but copies should not be included unless they are necessary to illustrate deficiencies. Some technical details may be included (e.g., the wavelengths for UV maxima or a short list of the M/Z values (and % peak height) from MS.)

- Where applicable, a summary of the evidence for

  - establishment of chirality
  - absolute configuration
  - morphology
  - particle size.

**Attachment B**

Spectra or X-ray diffraction patterns need not be included, unless they are necessary to illustrate deficiencies.

- Miscellaneous (other pertinent information)

## II. MANUFACTURER/TESTING FACILITIES

State the name, address, and responsibility of all facilities involved in the preparation (including testing) of the material which is the subject of the DMF. Include the Central File Number (CFN) and/or drug registration number, if available

## III. SYNTHESIS/METHOD OF MANUFACTURE

A. Starting Materials

The following items should be included in the review:

- Qualification as Starting Material: Include
  1. Evidence that the starting material meets the DSG criteria or
  2. Reference to a DMF describing its manufacture.

- Acceptance Testing: Summarize, including identity test and evidence to exclude isomeric analogues and/or impurities.

B. Solvents, reagents, other materials.

The complete list of the materials used in the synthesis need not be included in the review.

Identify any materials which may present concerns about:

- Safety (e.g., use of sulfite late in the synthesis). Such materials will need either evidence of removal, or appropriate control through specifications for the drug substance. (The appropriate review team member should be alerted to the existence of a possible safety issue.)

- Impurities (e.g., material that contains a substance that must be controlled to limit side reactions). In such cases a description of the testing of that material should be included in the review.

**Attachment B**

Re-use or recycling of materials (e.g. solvents, catalysts, or column materials) should be described and evaluated. Specify whether recycled solvents are used for any other process (please describe) or dedicated to the process described in the DMF.

Details of specifications should be included only to illustrate deficiencies.

C. Flow Chart

Include a copy of the flow chart of the synthesis.

D. Detailed Description

Include sufficient detail to permit critical analysis of key elements of the synthesis. Do not simply list the "name" reactions and chemical names/code numbers of intermediates or copy the holder's description.

The following items should be included in the review:

- Batch size
- Brief summary of each step, including:
  - Materials used (list the quantities only if necessary to illustrate a deficiency)
  - Reaction conditions (e.g., times and temperatures);
  - Isolation or purification process (if applicable)
  - Yield (if applicable)
- Final crystallization or purification solvent (where applicable).
- Location of executed batch records, if provided. The requirement for submission of executed batch records is a matter of Division policy.

## IV. PROCESS CONTROLS:

A. In-Process Tests

Include the tests performed to demonstrate adequate control of the synthesis (e.g., maintenance of proper pH to control side reactions or reaction completion by TLC). Include the step, purpose, and specification.

B. Specifications for Intermediates

**Attachment B**

Include summaries (and page references) of specifications for isolated intermediates. See the DSG for recommended information about intermediates.

The following items should be included for each intermediate:

- Identity by
  -chemical name/code number
  -synthesis step
- Test name and code number (if applicable)
- Specification (including chiral purity, if applicable)
- Page reference.

If appropriate process controls are not provided, this should be noted as a deficiency.

C. Reprocessing

Describe any reprocessing or re-working done during the preparation of the drug substance (e.g., re-chromatography of impure fractions or repeat of a reaction).

## V. REFERENCE STANDARDS

List the source of each reference standard (including those for impurities) and identify the standard used to qualify an in-house (working or secondary) standard. For primary and secondary standards for non-compendial items, and for in-house standards for compendial items, include:

- Any preparative procedures which differ from the manufacturing procedure in Section III, including any additional purification steps. If an alternate synthesis is used it should be described. For impurity reference standards prepared by the holder, include a summary of the whole preparative procedure.

- The basis for qualifying the reference standard.

- Any specifications which differ from the release specifications for bulk production material (see Section VI.). For impurity reference standards, include a summary of specifications.

## VI. SPECIFICATIONS

A. Description

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USP item: It is not necessary to include monograph methods for USP items. However additional tests and alternate methods should be included. For example, a particle size test (not in the monograph), an additional impurity test, or an alternate HPLC assay method may be used to qualify the material.

Non-USP item: All specifications including USP tests (e.g. <231> Heavy metals) should be included in the review for evaluation.

If a stability-indicating test is used which is different from the release test, this information should be included under "VIII. Stability."

The following items should be included for each specification (a table is recommended):

1. Identification of the test
2. Acceptance criterion
3. Procedure
    a. Code number (if applicable).
    b. USP citation (if applicable).
    c. An abbreviation to indicate the type of method (e.g., HPLC, IR).

**Attachment B**

4. Location in DMF

Example of Summary Table for "Cure-all" drug substance

| Test | Acceptance Criteria | Procedure | VOL.,PAGE REF. |
|---|---|---|---|
| Identity | a) IR conforms<br>b) chloride test | SAM 123 (KBr)<br>SAM 246 per USP <221> | 1.3, p 00125-7<br>1.3, p 00128 |
| Assay | 98.0 - 101.5%, anhyd. | SAM 456 (HPLC) | 1.3, p 00129-140 |
| Impurities | NMT 0.2% X-34<br>NMT 0.1% X-37<br>NMT 0.1% Other Single Impurity<br>NMT 1.0% Total Impurities | SAM 789 (HPLC) | 1.3, p 00140-200 |
| Water | NMT 0.5% | SAM 234 (KF) | 1.3, p 00201 |
| Residual Solvents | NMT 0.2% ethanol | SAM 235 (GC) | 1.3, p 00202-209 |
| Heavy Metals | NMT 20 ppm | SAM 236, per USP <231> | 1.3, p 00210-212 |

See discussion of "Impurities" below.

For each procedure include the following (a table is recommended for chromatographic methods):

- Name of Procedure: Include code number (where applicable)
- Description: (In one of the following formats):
  - A brief description (e.g., Identity: IR using KBr pellet) or
  - A brief narrative paragraph (e.g., HPLC using *column type*, with a *type of detector* and *a specified flow rate*, etc.) or
  - A list (e.g., HPLC:
    column type/length
    flow rate
    temperature
    mobile phase
    detection
    injection volume
    standard(s)

**Attachment B**

retention time(s)
sample preparation
system suitability tests)

- Validation: List the specific parameters evaluated (e.g., ruggedness, precision).

- Justification: Summarize the data used to justify the acceptance criteria.

Do not include copies of the method, calculations or spectra unless they are necessary to illustrate deficiencies.

**Attachment B**

Example

| Assay of "cure-all" by HPLC Method SAM 456 pp. 00129-140 | |
|---|---|
| Parameter | Description |
| Column | Nova-Pak $C_{18}$ (Waters), 15 cm X 3.9 mm |
| Mobile Phase | acetonitrile/methanol/0.05M Acetic acid + 0.02M $Et_3N$ buffer, 45:15:40 |
| Flow | 1.8 mL/min |
| Temperature | 30°C |
| Detection | 254 nm UV |
| Inject | 25 $\mu$L |
| Standard | Dissolve Reference Standard Cure-All in Methanol.1 mg/100 mL. Dilute to 1 µg/mL with mobile phase. Prepare 1 µg/mL X-37 (dihydrodiol) for resolution test. |
| Retention Times | Cure-all : 10-10.5 minutes |
| Sample Preparation | Dissolve in 200 mL mobile phase |
| System Suitability | pp 00137-8. |
| Resolution | NLT 1.5 between cure-all and X-37 [dihydrodiol]; |
| Reproducibility | Coeff.Var = NMT 2% (n = 5); |
| Tailing Factor | NMT 1.2 |

Validation: pp 00141-199. Tested for ruggedness, precision, accuracy, and reproducibility

Data to justify specification: Five batches tested. Content of cure-all = 98% (RSD= 1.1.%)

Evaluation: The preparation of the mobile phase is not clear. The amount of 0.02M

**Attachment B**

$Et_3N$ buffer is not adequately described.

DEFICIENCY: The holder should describe how much of the 0.02M $Et_3N$ buffer is used to prepare the mobile phase in the Assay method SAM 456.

Summarize the data for all tests for all batches analyzed.

B. Impurities

Include information about "Specified" (both identified and unidentified impurities) and "Unspecified" impurities. Refer to the section on “Stability” for stress testing used to identify potential degradants and for stability-indicating tests which are different from the release tests.

For each impurity include (where available):

- Identification: This will usually be a code number and should include the chemical names and structures, if available. If the chemical name is not known, another means of identification, such as the Retention Time on chromatography should be included. Impurities which have been described elsewhere in the review need only be listed by name or code number.
- Type (e.g., organic, inorganic): See ICH Guideline, "Impurities in New Drug Substances", for a discussion of the definition of impurity types.
- Source (e.g. synthesis, degradation)
- Page reference
- Assay method
- Limit

C. Microbiology

Microbiological test procedures may require a consult review if the drug substance:

- Is sterile
- Is of plant or animal origin, or
- Is derived by fermentation or biotechnology, or
- Is thought to support microbial growth.

## VII. CONTAINER/CLOSURE SYSTEM

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Include a description and acceptance tests for the container/closure system(s) components used for storage and shipping (e.g., 10 mil PE bag, double bagged, sealed by twist tie, placed in fiberboard container, and sealed with a snap-ring closure.)

Include the status of the materials used in the construction of each packaging component used in the primary packaging system.

Summarize the data showing that the container/closure system is compatible with the drug substance and is adequate to maintain drug substance stability. Refer to appropriate CDER Guidance documents.

## VIII. STABILITY

The stability information should be briefly summarized and evaluated, including stress and/or accelerated testing.

Include a list of potential degradants and the rationale for establishing a specification for individual degradants.

The following items should be included in the review:

- Protocol
  - Test intervals
  - Storage conditions
  - Container/closure system(s)
- Information about lot(s) tested
  - Identification
  - Synthesis scale (e.g., bench, pilot, production)
- Retest and/or expiration dating period
- Data which shows a significant change or trend
- Evaluation of stability-indicating assay method and validation information, if different from release method

For additional guidance please refer to appropriate CDER guidance documents concerning stability.

## IX. LABELING

Any deficiencies should be noted.

**Attachment B**

## X. COMMENTS AND LIST OF DEFICIENCIES

Compile a list of all deficiencies found in the review. This may be in the form of a draft letter.