OFFICE OF PHARMACEUTICAL SCIENCES

COVER FORM FOR THE TECHNICAL REVIEW OF DRUG MASTER FILES (DMFs)

CONTENTS

PURPOSE This MAPP establishes Center policy and procedures for using a cover form for the technical review of drug master files (DMF).

BACKGROUND

Since DMFs are reviewed by CDER in support of a number of different submissions to the Agency, it is important to keep consistent, accurate records of DMF reviews. A standard cover form will facilitate the collection of information during DMF reviews for entry into a database in standard format.

REFERENCES

- 21 CFR 314.420, Drug master files
- Center for Drug Evaluation and Research, *Guideline for Drug Master Files*, (09/89)

DEFINITIONS

- **Applicant**. The company or entity that submits an application.
- **Application.** For the purposes of this MAPP, an investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), DMF, or export application that references the DMF.
- **Contact Person.** The individual to whom correspondence to the DMF holder should be addressed.
- **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.
- **Holder**. The company or entity that submits a DMF.
- **Letter of Authorization (LOA).** A letter from a DMF holder that authorizes another applicant to incorporate by reference all or part of the contents of their DMF in support of an application and authorizes FDA to review this information.
- **Primary DMF.** A DMF that references another DMF.
- **Representative.** A third party (usually a company) that acts on behalf of the holder in its interactions with the Agency. For a foreign firm this party is often referred to as the "US Agent."
- **Secondary DMF**. A DMF that is referenced by another DMF.
- **US Agent.** A company or agent resident in the United States appointed by a foreign firm to act as their representative.

POLICY The DMF cover form (Attachment A) should be completed and included as the first page(s) in every written review of a DMF.

PROCEDURES

- A DMF review should be written in such a way that it clearly documents the adequacy of the information in the DMF to support an application. A completed DMF Cover Form

(Attachment A) should be included as the first pages(s) of the review. Instructions for completing a DMF cover form are provided in Attachment B.

- DMF reviews should be filed with the original and duplicate DMF jackets. A copy of the DMF review may be filed in a division or office file. The DMF review or any information found in the DMF (except for information in the LOA) should ***not*** be included in or attached to the review of an application referencing the DMF.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A

DMF REVIEW COVER FORM

DMF Number: **DMF Type**:
TITLE:

1. CHEM REVIEW No. **2. REVIEW DATE:**

3. ITEM REVIEWED

A. IDENTIFICATION
- USAN
- Ingredient Dictionary name
- Trade name
- Manufacturer's code
- Chemical name
- CAS number, if available.

B. LOCATION IN DMF

Type of Submission	**Date of Submission**	**Location of Information**

4. PREVIOUS DOCUMENTS

Type of Document	**Date of Document**	**Location**	**Description**

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE or US AGENT (if applicable):
NAME:
ADDRESS:

CONTACT PERSON'S NAME, TITLE, DEPARTMENT:
ADDRESS:
TELEPHONE NUMBER:

6. DMF REFERENCED FOR:

NDA\ANDA\AADA\IND:
PRIMARY DMF (as needed)
APPLICANT NAME:
LOA DATE:
DRUG PRODUCT NAME:
DOSAGE FORM: CODE:
STRENGTH:
ROUTE OF ADMINISTRATION: CODE:

7. SUPPORTING DOCUMENTS:

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF:
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:

9. CONSULTS:

10. COMMENTS:

11. CONCLUSION:

Appropriate signature block and cc list.

Attachment B

INSTRUCTIONS FOR THE USE OF THE DMF REVIEW COVER FORM

General Instructions

1. Do not change the order or delete any sections. Sections that do not apply should be marked "N/A."

2. It may be appropriate to adjust the spacing between sections to accommodate necessary information, such as a chemical structure or a long listing of NDAs under Item 6.

3. Dates should be in the DD-MMM-YYYY format to conform with the COMIS DMF listing (e.g., 31-MAR-1994).

4. The DMF cover form is an integral part of the review and, as such, should always be part of the review documentation, both physically and electronically. The information entered into this form will be used to identify the scope of the review for entry into the COMIS data base, drafting of correspondence, and information for future reviewers. Where possible, information should be scanned rather than photocopied so that the review is complete in electronic format. Chemical structures may be created with chemistry drawing software.

The following sections will be entered into the COMIS data-base:

3. ITEM REVIEWED
   - A. IDENTIFICATION
   - B. LOCATION IN DMF

6. DMF REFERENCED FOR
10. COMMENTS
11. CONCLUSION:

Please make sure the information in these sections is accurate and complete.

1. REVIEW

Each review for a particular item in a DMF should be numbered sequentially even though the reviewer may be different. Reviews of different items in the same DMF should have separate numbering sequences i.e., reviews of Rubber Formulation A in DMF XXXX will be numbered separately from the reviews of Formulation B in the same DMF. Reviewers should check for previous reviews in COMIS and in Excalibur.

2. REVIEW DATE

This should be the date when the reviewer completes the review of the submissions listed. This is the date that will be entered into the electronic DMF system, as opposed to the "Review Stamp Date," which is entered separately.

3. ITEM REVIEWED

Because DMFs often contain information about a number of different items and also may contain numerous amendments, it is important to identify the item being reviewed and the location of the information in the DMF. Please note that the "Subject" or

"Title" of the DMF is entered in the heading of the Cover Form.

A. Identification: Provide all names that uniquely identify the item. For reviews of DMFs that are not concerned with the preparation of chemical substances, provide a description of the information reviewed (e.g., toxicology studies on compound X in rats). For chemical substances, enter the following, as applicable:

USAN
Ingredient Dictionary name (available on COMIS). If there are questions about the name in the Ingredient Dictionary, contact the Division of Data Management Services.
Trade name
Manufacturer's code
Chemical name
CAS number, if available.

If there is no USAN enter another "Listed Name," such as a British Approved Name (BAN), noting that it is BAN, INN, etc.

Use the chemical name (CAS or IUPAC) only if there is no USAN or ingredient dictionary name.

If a particular synthetic process to obtain a drug substance is reviewed, this should be specified (e.g., "compound X synthesized by procedure A").

B. Location of DMF information: All sections of the DMF reviewed should be specified by type of submission, volume, page, and date. Under "Type of Submission," specify whether it is an Original Submission, Amendment, Amendment in Response to Letter, Total Update, or Annual Report.

4. PREVIOUS DOCUMENTS

Provide a list of relevant documents, including both holder and FDA-generated documents, where appropriate. The purpose of this list is to enable the reader to know where relevant information concerning the item under review may be found in the DMF. It is unnecessary to include the entire history of the DMF. The type of document (e.g. amendment, review), the date of the document (not the stamp date), and a brief description of the document should be provided. The extent of this list is at the discretion of the reviewer. If the list is extensive, it may be included as an appendix.

Example:

Type of Document	**Date of Document**	**Location**	**Description**
Amendment	06-Feb-1995	Vol 2.1	Add formulation of Resin A
Review #1	26-Jul-1995	Vol 2.1	Review of 06-Feb-1995 Amendment
Deficiency Letter	28-Jul-1995	Vol 2.1	Deficient for test methods for Resin A
Telecon	01-Aug-1995	Vol 3.1	Clarification of deficiencies

5. NAME AND ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S)

Include the complete address of the holder. This may be an administrative office that is different from the actual manufacturing site.

If a DMF holder has designated a third party to act as its representative (US Agent for a foreign firm), the name and address of the representative also should be listed.

CONTACT PERSON: Provide adequate information to permit correct addressing of correspondence. If a contact person is not specifically identified, enter the name of the individual who signed the cover letter for the DMF.

6. DMF REFERENCED FOR

If there are multiple applications under review that reference the DMF, it is preferable to present the information in tabular form.

Inappropriate application types should be deleted from "NDA/ANDA/AADA/IND." If the application supported by the DMF is a supplemental NDA include the supplement number.

If a DMF is reviewed in support of another DMF ("Primary DMF"), this should be noted. Include the information concerning the application that referenced the primary DMF in the other parts of this section. Use the date of the LOA from the holder of the secondary DMF, not the date of the LOA from the holder of the primary DMF.

The dosage form (DF) and route of administration (ROA) are listed to allow future reviewers to see, from examining the COMIS listing, whether the review is applicable to the DMF referenced for their application. Please refer to the list prepared by the CDER Nomenclature Standards Committee for information on naming DFs and ROAs. The list of DFs and ROAs (with their corresponding code numbers) may be found in the CDER Standards Manual and on the CDER Common Drive (X: drive in ONDC, Y: drive in OGD) . The list is updated periodically. At the time of the issuance of this MAPP these are located in x:\workgrps\terms\drg00201.wpd (Dosage Forms) and x:\workgrps\terms\drg00301.wpd (Route of Administration). The location of these files may change in the future.

7. SUPPORTING DOCUMENTS

Include DMFs for raw materials or intermediates or other appropriate documents, if necessary.

8. DMF CURRENCY

In the *Guideline for Drug Master Files* and in the letter acknowledging receipt of a DMF, it is stated that a holder should update the complete list of persons authorized to incorporate information in the DMF by reference annually and provide an annual report that identifies all changes since the last annual report or provide a statement that the previously submitted information remains current. If the holder has not updated the DMF for a number of years, then the information in the DMF may not be reliable. The list of firms authorized to reference the DMF is usually provided in the Annual Report.

9. CONSULTS

Identify the date, the office consulted, the material/sections sent, and the status of the consult.

10. COMMENTS

This information will be entered into the COMMENTS field in COMIS for the benefit of future reviewers. The COMIS DMF data query screen has not been updated to permit viewing of the field for "Item Reviewed" so reviewers should identify the item(s) reviewed in the "Comments." Provide a listing of the status of pending consults and a brief summary of the areas in which deficiencies have been noted. This section should not be a lengthy itemized recap of deficiencies identified in the review. If previous deficiencies have been corrected, refer to previous letter. If there are no deficiencies, this field should be left blank, except for an identification of the item(s) reviewed (see above). The field can accommodate 240 characters.

Example:
Reviewed drug substance X. Inadequate for synthesis, packaging, stability. Send Deficiency Letter.

11. CONCLUSION

If there are no deficiencies in the DMF, the entry should be "ADEQUATE," the term used in COMIS. If there are deficiencies this entry should be "INADEQUATE."

SIGNATURE/CC. BLOCK

A signature and cc. block should be included at the end of the cover form or chemistry review depending on the procedures normally employed in the review division. Two copies of the review should be sent to the DMF jacket. Do not send a copy of the review to the application that references the DMF.

ATTACHMENT C

SAMPLE DMF REVIEW COVER FORM

DMF Number: **DMF Type**: III
Title: Polypropylene Resins

1. CHEM REVIEW #: 2 **2. REVIEW DATE:** August 3, 1994

3.ITEM REVIEWED

A. IDENTIFICATION
Formulation 42
Chemical Name: Polypropylene resin

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Amendment	March 23, 1994	Volume 1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location	Description
Original	06-Feb-1981	Vol 1.1	List formulation names
Amendment	25-Feb-1984	Vol 2.1	Add Formulation 41
Review #1	25-Apr-1987	Vol 2.1	Deficient for Formulation 41
Deficiency Letter	27-Apr-1987	Vol 2.1	See Review #1
Annual Update	05-Mar-1994	Vol 3.1	

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):
NAME: Bigtime Polymers
ADDRESS: Main Street
Anytown MA 20315
CONTACT PERSON'S NAME and TELEPHONE NUMBER: John Doe, 617-555-4444

6. DMF REFERENCED FOR:
NDA: NN-NNN
APPLICANT NAME: Big Drug Company
LOA DATE: March 23, 1994
DRUG PRODUCT NAME: Cureall
DOSAGE FORM: Solution CODE:138
STRENGTH: 10 mg/mL
ROUTE OF ADMINISTRATION: Oral CODE:001

7. SUPPORTING DOCUMENTS: N/A

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: 05-Mar-1994

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 05-Mar-1994

9. CONSULTS: N/A

10. COMMENTS: Deficient for manufacturing procedure and specifications.

11. CONCLUSION: Inadequate

Review Chemist, HFD-YYY

Chemistry Team Leader, HFD-YYY

cc:
DMF XXXX (2 copies)
HFD-YYY/Division File NDA NN-NNN
HFD-YYY/PM
HFD-YYY/TeamLeader
R/D Init by:
F/T \Wp: c:\chem\D\0XXXX408.1RC