The International Pharmaceutical Excipients Council of the Americas

Excipient Master File Guide

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ACKNOWLEDGEMENTS

This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). IPEC-Americas is a U.S. based industry association comprised of excipient manufacturers and their pharmaceutical customers. The contributing individuals are listed below.

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TABLE OF CONTENTS Pages

Pages

ADMINISTRATIVE SECTION

1. SCOPE

The focus of this guide is the United States; however, the intent is to develop a guide with global application.

A Type IV Excipient Drug Master File (DMF[1]) is a submission to FDA containing information that may be used to support an Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biological License Application (BLA), Veterinary Drug Application, another DMF, or an Export Application.

An Excipient DMF should follow the harmonized structure and format of the ICH Common Technical Document (CTD) for presenting chemistry, manufacturing, and controls and safety information. This same information can be used for marketing authorization applications worldwide.

An excipient is defined as any substance other than the active pharmaceutical ingredient (API) in a drug product which has been appropriately evaluated for safety and functionality and is included in a drug delivery system. Excipients may be used to aid in the processing of the drug substance during manufacture, to protect, support or enhance stability and bioavailability. DMF's can cover excipients that may be comprised of single ingredients, mixtures or co-processed materials. Each type of excipient may require a slightly different approach when establishing the design of the DMF to facilitate the review process by FDA (the Agency).

2. GENERAL INFORMATION

There are many administrative responsibilities for the Agency and the DMF holder such as processing of the DMF documents and the filing of letters of authorization and annual updates.

An Excipient DMF is not required by law or FDA regulations. It is submitted solely at the discretion of the holder. It is not approved or disapproved. The DMF is maintained as a confidential document that cannot be submitted to third parties without the written agreement of the excipient ingredient manufacturer. The DMF contains manufacturing and controls information and technical data to support the safety and quality of the excipient.

If an agent is appointed (person appointed by a DMF holder to serve as the contact for the holder), the DMF must contain a signed letter submitted to the FDA stating the agent's name, address, and scope of responsibilities.

[1] Type IV DMF

A Statement of Commitment is a signed statement by the DMF holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

The holder of the DMF for an original submission receives an acknowledgement from the FDA assigning a number to the DMF once filed.

The DMF must be in the English language. Whenever a submission contains information in another language an accurate English translation must be included.

3. MAINTENANCE AND MANAGEMENT OF CHANGE

The regulatory responsibilities of a DMF holder are cited in 21CFR 314.420. A DMF is required to contain the listing of persons authorized to refer to a DMF. If the DMF holder adds, changes, or deletes significant information in the file (except annual updates of authorized users) the holder shall notify in writing, each person authorized to reference that information.

There are 2 types of subsequent communication to the Agency concerning the DMF; a report informing the Agency of a significant change in the manufacturing process and the annual report. The DMF holder should evaluate all changes in the manufacture of the excipient from that previously listed in the DMF using the provisions of IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients.* If the change is found to be significant, the Agency must be notified promptly. Otherwise there should be an annual report to the Agency clearly identifying all changes and additional material incorporated into the DMF since the last report was filed. The report to the Agency, either reporting a significant change or annual report, must include a transmittal letter concerning the specifics of the update and should contain the complete Letter of Authorization (LOA) list. If there is no annual report for the DMF filed for 2 consecutive years, the FDA has the right to consider the DMF inactive.

The IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients* establishes uniform considerations for evaluating the significance of changes involving the manufacture of bulk pharmaceutical excipients (BPE). The purpose of the evaluation is to determine the need for informing the excipient customer and regulatory authorities about the nature of the change.

A significant change is any change that alters an excipient's physical or chemical property from the norm or that is likely to alter the excipient performance in the dosage form. In addition, potential effects on the safety of the excipient should be evaluated.

The IPEC-Americas Guide discusses the levels of change and should be referenced for evaluating change.

Use of the IPEC-Americas Guide will assist in determining the change risk level and therefore the documentation and notification requirements.

4. TRANSMITTAL LETTERS

Transmittal letters to the FDA accompany the DMF to the Agency and instruct the Agency as to the nature of the submission. A transmittal letter serves one of three purposes. It instructs the Agency that this is:

1. An original submission and the Agency should assign a DMF number and hold the DMF for future reference in the filing of an application for a drug product.

2. The submission is an amendment to a DMF on file with the Agency. The letter provides instructions on updating the DMF.

3. The letter is an affirmation that the DMF holder has reviewed the DMF and found that no amendment is necessary.

4.1 Original Submissions

An original submission should include the following information:

- Identify submission: original, the type of DMF (Type IV) and its subject.
- Identify applications, if known, that the DMF is intended to support. Include the name and address of each sponsor, applicant, or holder, and all relevant document numbers.
- Signature of the holder or authorized representative
- Typewritten name and title of the signer
- Original submission of a DMF should contain the name and addresses of the following:

    1. DMF holder

    2. Corporate headquarters

    3. Manufacturing/processing facility

    4. Contact for FDA correspondence

    5. Agent(s), if any

    6. The specific responsibilities of each person listed above

4.2 Amendments

- Identify the submission: Amendment, the DMF number, type of DMF (Type IV), and the subject of the amendment.

- A description of the purpose of the submission, e.g., updates, revised formula, or revised process.
- Signature of the holder or authorized representative.
- When an amendment is submitted reporting a significant change that is expected to require a supplement for applications using the excipient, a new letter of authorization (LOA) may be submitted for each item affected by the change.

4.3 Annual Updates

Annual updates should be submitted, even if there is no change reported. The update should contain a list of companies authorized to reference the DMF, including the date of the LOA and the item referenced (in situations where a DMF contains multiple items).

5. LETTERS OF AUTHORIZATION

The DMF holder should submit in duplicate to the FDA a letter of authorization (LOA) permitting FDA to reference the DMF on behalf of a pharmaceutical sponsor who has included the excipient in their drug application. The LOA should include the following:

1. The date
2. Name of DMF holder
3. DMF number
4. Name of person(s) authorized to incorporate information in the DMF by reference
5. Specific product(s) covered by the DMF
6. Submission date(s) of 5, above
7. Section numbers and/or page numbers to be referenced
8. Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
9. Signature of authorizing official
10. Typed name and title of official authorizing reference to the DMF.

- The holder should also send a copy of the LOA to the affected applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF. The applicant, sponsor, or other holder referencing a DMF is required to include a copy of the DMF holder's LOA in the application.

CORE TECHNICAL DOCUMENT

1. SUMMARIES

The purpose of the Core Technical Document is to harmonize the organization of the quality section of the DMF so that this section will be acceptable in the CTD format.

The ICH guide for the Common Technical Document specifies that the DMF should be prepared with margins sufficient to allow for printing on A4 paper (E.U. and Japan) and 8.5 x 11" paper (U.S.). The left-hand margin should be wide enough to accommodate the binding of the DMF. The style and size of the font should make the report legible even after photocopying. Times New Roman font, in 12-point is recommended. Finally any acronyms and abbreviations should be defined the first time they are used. Appropriate binders should be used for the Drug Master File as specified by the FDA.

2. DESCRIPTION, CHARACTERIZATION AND INTENDED USES

Establishment of a meaningful physicochemical profile of pharmaceutical excipients is fundamental to evaluating their suitability for use and maintaining the quality of both excipients and products of which they are constituents. The DMF will include a chemical characterization of the substance which may include the chemical structure where appropriate. It is generally expected that methods used to establish these profiles will be more extensive than those used to control the identity, quality, and purity of the excipient on a routine basis, but may be similar to those used to characterize reference standards.

Biologic excipients present special challenges in their characterization. In order to ensure consistency in the quality of the excipient, often it is necessary to develop a thoroughly characterized reference standard or to compare the excipient to its natural counterpart. The physicochemical characterization of the biologically derived excipient should include the composition, physical properties and structure. Where the excipient is heterogeneous, the composition of the mixture should be ascertained. For further guidance on biologics, see the ICH guideline on biotechnological/biologic products.

2.1 Intended Use

A Statement of Intended Use may be included. If there is an application for which the manufacturer does not intend the excipient to be used, it should be stated.

If a Statement of Intended Use is included it may contain:

1. For human and/or veterinary uses.

2. The route(s) of administration for intended use.

3. The maximum daily dose for human or veterinary route of administration for the pharmaceutical excipient.

4. A general description of the intended function and mechanism of action.

2.2 Characterization of Excipients

Where possible, reference to an excipient monograph from the USP/NF, FCC or other official source is adequate and further characterization of the excipient is generally not required. However, if new, substantially different methods of manufacture, or source materials are employed, confirmation of identity and evaluation of the excipient impurity profile should be conducted. Such confirmations may be limited to proof of conforming structure (including isomerism and polymorphs where appropriate) and quantitative evaluation of process and starting material impurities. Where such impurity data is provided, detailed methodology and supporting validation should be provided for non-official analytical methods. If there are questions as to whether a source of a standard would be considered by FDA to be an official source, applicants should contact the appropriate chemistry review staff at the FDA.

Due to the diverse nature of substances which may be incorporated as pharmaceutical excipients, including highly complex mixtures from animal and/or botanical sources, differing approaches to characterizing their properties may be required. Pharmaceutical excipients may consist of either individual or limited combinations of discrete and identifiable molecular entities (non-complex), or may consist of highly complex entities either individually or in mixture from animal, botanical, synthetic or semi-synthetic sources (complex).

An excipient that does not have a monograph in the USP/NF, FCC or other official source should be thoroughly characterized. Generally, the following characterization information should be considered:

1. For pharmaceutical excipients composed of more than one discrete and identifiable entity, a quantitative and qualitative description of the mixture, including any special characteristics such as co-processing or coating.

2. Appropriate chemical attribute information, such as structural formula, empirical formula, molecular weight or molecular weight ranges, as well as, potential isomerism and/or polymorphism. Information to substantiate the proof of structure should include appropriate analytical tests, such as elemental analysis, infrared spectrophotometry (IR), ultraviolet spectrophotometry (UV), optical rotation, nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS), as well as applicable functional group analysis. Detailed interpretation of the test data in support of the claimed structure should be provided.

3. Legible reproductions of the relevant spectra, chromatograms, thin-layer chromatogram (TLC) photographs or reproductions, and other appropriate instrumental recordings.

4. Data establishing purity. The data should be obtained by using appropriate tests, such as TLC, gas chromatography (GC), high-pressure liquid chromatography (HPLC), phase solubility analysis, appropriate thermometric analytical procedures, and others as necessary.

5. A physical description of the material, including its color and physical form.

6. Appropriate physical constants such as melting range, boiling range, refractive index, dissociation constants (pK values), and optical rotation.

7. A detailed description of the analytical procedures used to characterize each component of the pharmaceutical excipient.

It is recognized that some excipients may be difficult or impossible to fully characterize by analytical means. In such circumstances considerably greater attention may be given to establishing and maintaining control of the source materials and manufacturing process. For excipients that are biological in nature or derived by biological processes, it may be appropriate to include basic physicochemical and biological information. For further details, consult the FDA's guidance documents.

3. FACILITIES DESCRIPTION

The only information that should be included is the actual location (address) and the contact person.

4. MANUFACTURING

4.1 Origin of Starting Materials

A summary of the origin of all starting materials should be provided in appropriate detail. A summary of processing of starting materials which may provide for the inactivation of potential pathogens and/or contaminants may be provided.

4.2 Manufacturing Process

This section should include a process description that sufficiently describes the manufacturing process and the raw materials used in the manufacture of the excipients included in the DMF. The process description should be presented by a process flow diagram, as well as a written description to facilitate understanding of details. All of the key processing steps should be represented with sampling points indicating the points of the process where changes can be made.

The type of excipient and the specific manufacturing process used is important to evaluate when developing information for inclusion in an excipient DMF. The level of detail needed and the type of information to be submitted should be dictated by the complexity of the manufacturing process. The objective of this section of the DMF is to provide the FDA reviewer with a clear understanding of the manner in which the

excipient is produced. Also to be referenced is whether the process is open or closed, batch or continuous or a combination of these scenarios. The process should be described with enough detail to clearly present the main operational steps, the key equipment used and identify the primary control points.

Packaging operations should be included as part of the process and may be done at other locations. These locations and representation of those processes should be included or referenced if they are part of another master file. The type of packaging used in the storage and distribution of the product is an important part of the manufacturing process.

Significant changes to any part of the process, as described in the DMF, should be reflected in an update/amendment to the drug master file. The IPEC Significant Change Guide for Bulk Pharmaceutical Excipients should be used as the basis to determine when a change is considered significant.

5. PROCESS CONTROLS DURING MANUFACTURE AND PACKAGING

A comprehensive description should be provided for the manufacturing process and material controls used along with the location of the controls. Criteria and results determining the protection and safety of the containers, closures and components should be described along with labeling system controls.

6. SPECIFICATIONS

The excipient should be identified and characterized by its specifications.

These specifications should be consistent with the product's labeling (including any compendial requirements if claimed) and/or its statement of intended use if included. The specifications should be based on scientifically sound development work, and should be sufficient to ensure the material's identity, purity, physical form, stability, and sterility where applicable.

"A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described."[2] When the excipient is produced in conformance with a monograph, the excipient specification should include all monograph test requirements. Additionally, the test methods used by the manufacturer should be validated to demonstrate they provide comparable results to the monograph test method.

The specification for an excipient that is not produced in conformance to compendial requirements should contain, at a minimum, the following:

[2] ICH Harmonised Tripartite Guideline, *Specification: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, pg 1.

1. Description: A statement as to the physical form of the excipient under ambient conditions.

2. Identification: A test able to discriminate the excipient from similar substances. Suitable identification tests include infrared spectroscopy, HPLC/MS, GC/MS etc.

3. Assay: A specific method or combination of methods capable of demonstrating the purity of the excipient. Where direct measurement of purity is not feasible, then measurement of impurities may be suitable.

4. Impurities: Methods should measure the presence of organic and inorganic impurities as well as the presence of residual solvents, where applicable.

5. Water Content: Karl Fischer moisture or loss on drying should be specified where the presence of water will affect the functionality of the excipient or the drug product.

Physicochemical tests such as pH, viscosity, residue on ignition, and specific heavy metals should be included where warranted. Tests to define particle size, film granularity, or other appropriate physical attributes should also be considered.

Microbial limits should be considered for excipients that can support growth or where the excipient is offered for sale in drug products that bypass the body's natural defenses, such as ocular or parenteral applications. Microbial techniques can be used to demonstrate that the excipient will not support microbial growth and thus need not be tested in this manner.

7. REFERENCE STANDARDS FOR MATERIALS

Where applicable, provide the source and details of the reference standards.

8. BATCH ANALYSIS

Information on representative batch analysis should be provided based on defined product specifications. Some of the typical additional information included would be: batch number, manufacturing date, batch size, etc.

9. CERTIFICATE OF ANALYSIS

A sample certificate of analysis (COA) should be included. The COA is generated from batch record data or a final batch. The source of the data for the COA should be referenced. IPEC's Certificate of Analysis Guide should be the basis for determining the design and content of the COA and can be referenced for additional information.

10. STABILITY

While many excipient products are very stable and may not require extensive testing to assure stability, the stability of excipients is an important contributing factor to the stability

of the finished dosage form. Some excipients may undergo chemical, physical, and/or microbiological changes over time that causes the material to fall outside established specifications. The stability of excipients may be affected by undetected changes in raw material specifications or subtle changes in manufacturing procedures. Excipients may be shipped in a large variety of different packaging types that can affect their stability (e.g., drums - metal and plastic, bags, bottles - plastic and glass, tankcars, etc.).

Typically, an excipient stability program involves the evaluation of the physical and chemical properties of the neat excipient.

Stability testing should determine whether possible degradation, moisture gain or loss, viscosity changes, or other possible changes occur to make the excipient unacceptable for use (e.g. unstable or hygroscopic materials).

Stability documentation should be included for the application of the excipient. The relevant ICH guidelines should be referenced. The IPEC GMP Guide for Bulk Pharmaceutical Excipients may be referenced for "model product" approaches to assess the stability of similar excipients.

Data from formal stability studies should be provided on at least three batches of the excipient. The batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. The overall quality of the batches of excipient placed on formal stability studies should be representative of the quality of the material to be made on a production scale. Other supporting data can be provided.

The stability studies should be conducted on the excipient packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

Stability studies should include specification testing of those attributes of the excipient including the impurity profile that are susceptible to change during storage and are likely to influence quality or safety. The testing should cover the appropriate physical, chemical, biological, and microbiological attributes. IPEC's Guide for the Development of an Impurity Profile should be consulted for additional information.

Testing frequency should be in the protocol depending on the product attributes that may be subject to change. Testing frequency is dependent on best known science of the anticipated change.

The testing program should include defined and controlled storage conditions for temperature and humidity and any other conditions that can be expected to alter the product. The ICH guidelines should be consulted for recommended conditions. The IPEC guide should be consulted if a significant change occurs.

If the need for special storage conditions exists (e.g., protection from light, heat, etc.), such restrictions should be placed on the labeling.

A storage statement should be established for the labeling in accordance with relevant national/regional regulatory requirements

The results of such stability testing should be used in determining appropriate storage conditions, re-evaluation or expiration dates. IPEC's Certificate of Analysis Guide should be consulted for additional information for expiration dates and recommended re-evaluation dates.

11. EXCIPIENT LABEL

A Type IV DMF should contain a copy of the label that appears on the immediate container used to transport the excipient. A separate label is needed for each grade of excipient covered by the DMF. For excipient mixtures, it may be appropriate to only include sample labels that are representative of a product group of similar mixtures. The label should be clear enough to permit distinguishing similar products.

Typically an excipient container label should contain, at a minimum, the following information (where applicable):

1. The trade name of the excipient.

2. The compendial designation of the excipient.

3. The grade of the excipient, where there are multiple grades.

4. The name of the excipient manufacturer and/or distributor.

5. The address of the plant of manufacture

6. The lot/batch number from which the complete lot history can be determined.

7. The gross/tare/net weight of the container.

The container label should also contain transportation and safety information in conformance with applicable laws and regulations.

Refer to the CFR for specific requirements and to the USP/NF for specific excipient labeling information.

12. NONCLINICAL SAFETY ASSESSMENT

The purpose of this section is to outline the relevant nonclinical information for safety evaluation of an excipient by its intended route of administration. The format of this section is flexible and is meant to reflect the general nature of the excipient under discussion:

1. New excipients

2. Existing excipients not fully described by monographs (includes excipient mixtures and modified physical forms)

3. New route of administration/application for existing excipients

4. Biotechnology-derived excipients

The toxicological assessment of impurities is also reviewed, as this is an area of concern for some excipients.

12.1 Introduction and Choice of Safety Assessment Guidelines

This section must clearly state the name of the excipient and toxicologically relevant impurities. In the case of an excipient mixture, all components and their percentages should be listed. Where applicable, it may be important to demonstrate that chemical interactions between the components have been minimized. It is recommended that all potential new excipients be evaluated in a standard battery of safety pharmacology tests (see ICH S7A ICH S7B). Physical/chemical properties, structure-activity information, and existing toxicology data should be considered when determining testing needs. These safety evaluations may be performed as part of the of toxicologicological/pharmacological evaluations of the formulated drug or as independent safety evaluations of new excipient.

A summary of the history of use and status of the excipient or constituent substances should be provided. This summary should include information such as the current use in food or other consumable products, current regulatory status in the country of filing (such as Generally Recognized as Safe (GRAS) status) as well as other countries, the status and use of any closely related products and/or predecessor products, and a discussion of, and reference to published scientific literature regarding the substance.

Toxicologically relevant impurities must be identified in this section. The definition of a toxicologically relevant impurity is an impurity that can be reduced to levels of no significant risk of adverse health effects, as well as having no adverse effect on stability or functionality, when used at typical use levels in a drug product. Assessment of impurities is further discussed in Section 12.3.

The safety assessment guideline used to determine the extent of the toxicology testing program for an excipient should be stated. Several publications have been written to outline the toxicology testing for new excipients. In the US, the IPEC-Americas Safety Committee has published a guideline for safety assessment of new excipients (Steinberg et al., 1997) which has been published as General Chapter <1074> in USP24/NF19. In Europe, Council Directive 75/318/EEC states that the toxicology and pharmacokinetics of an excipient used for the first time shall be investigated. In addition, IPEC-Europe has published a safety assessment guideline similar to that of IPEC-Americas (IPEC Europe

Safety Committee, 1996). The readers' attention is invited to the draft guidance, "Nonclinical Studies for Development of Pharmaceutical Excipients," currently being development by the FDA.

The IPEC-Europe publication discusses new uses for existing excipients. New uses for an existing excipient may include a new route of exposure (e.g. from dermal use to oral use) or higher use level by the same route of exposure. The administration of existing excipients to special populations (e.g. children and immunocompromised individuals) should also be considered in a safety assessment.

In the case of existing excipients, it is possible that extensive toxicology data are available, but these studies may not have been conducted according to current guidelines. The excipient manufacturer should assess the data and determine it's relevance to the intended applications.

The safety assessment of biotechnology-derived excipients (ICH 1997a) and existing excipients not fully described by monographs is determined on a case-by-case basis along with the discussion with the regulatory agency.

12.2 Route of Exposure & Estimated Daily Dose

Based on the current safety data, the general route of exposure of the excipient and maximum usage level in a dosage form should be stated in this section. If the excipient is used in only one special dosage form e.g. bolus intravenous formulations, then this should be stated.

In addition, every effort should be made to calculate an estimated maximum daily dose of the excipient. Exposure assessment of excipients by various routes of administration has been previously described in the literature (George and Shipp, 2000). Estimated maximum daily dose for most routes of exposure is reported in units of excipient/kg body weight/day, e.g. 10 mg/kg/day.

For excipient mixtures, the estimated daily dose can be determined by calculating the overall estimated daily dose and then multiplying by the percentage of each component. The estimated maximum daily dose for each component is used for safety assessment.

12.3 Impurities

An assessment of the impurities and degradants present in the excipient should be included along with what is known of their potential toxicological effects. This assessment should form part of the justification for proposed impurity limits in the excipient/drug product and be cross-referenced to the Quality section of the Drug Master File documentation. The ICH guideline on limits for impurities and residual solvents should be applied when these excipients are being developed (ICH, 1997b). Acceptable limits of impurities and residual solvents should be based on acceptable risk associated with exposure (ICH, 1997b). An acceptable limit is calculated based on the Permissible

Daily Exposure (PDE) that is derived from the no-observed-adverse-effect level (NOAEL) in the most relevant animal study as follows:

$$\text{Acceptable Limit (ppm)} = \frac{1000 \times \text{PDE (mg/day)}}{\text{dose g/day}^{1}}$$

PDE is given in terms of mg/day and dose is given as g/day. This may be applied if the daily dose is not known or fixed (for calculation of PDE refer to the ICH Guideline for Residual Solvents)

The implication of any differences in the impurity profile between the excipient used in the nonclinical safety studies and the product to be marketed should be discussed. If a new or biotechnology-derived excipient is being used in drug development, an assessment of information regarding its safety should be provided. Relevant scientific literature and the properties of relevant excipients should be taken in account. Assessments of toxicology data on impurities are also obtained from regulatory databases. Limits based on published safety data used to establish Permissible Daily Exposure should be discussed. The availability of information on the quality of batches used should also be discussed.

12.4 Nonclinical Safety Overview and Tabulated Summaries

This guideline is not intended to indicate what studies are required. The IPEC safety guide is the primary document used to make this determination. This guideline merely indicates an appropriate format for the nonclinical safety data that have been acquired (see ICH CTD Module 4). Applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

The evaluation of nonclinical safety studies should be arranged in a logical order so that all relevant data elucidating a certain effect are brought together. Extrapolation of the data from animals to human should be considered in relation to:

1. Animal species used
2. Number of animals used
3. Routes of administration employed
4. Dosages used
5. Duration of treatment or of study
6. Systemic exposure in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarizing this information are recommended.

[1] If dose is not known, assume a maximum daily dose of 10 g

7. The effect of the excipient observed in nonclinical safety studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The integrated Overview and Conclusions should clearly define the characteristics of the excipient as demonstrated by the nonclinical safety studies with conclusions supporting the safety of the excipient for the intended use. A NOAEL for the material should be established.

12.5 Toxicology Summaries

The written summaries of toxicology information should be in an acceptable format such as in the ICH CTD. Applicants can modify the format if needed to provide the best possible presentation of the information that will facilitate the understanding and evaluation of the results.

Whenever appropriate, age and gender-related effects should be discussed. Consistent use of units throughout the summaries will facilitate the review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

12.6 Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies. Species should be ordered as follows:

1. Rodents

2. Non-rodents

12.6.1 Routes of administration should be ordered as follows

1. The intended route for human use

2. Oral

3. Intravenous

4. Intramuscular

5. Intraperitoneal

6. Subcutaneous

7. Inhalation

8. Topical

9. Other

In some cases, tables and figures may be used in communicating effectively.

12.6.2 Nonclinical Safety Summary

The sequence of the Nonclinical Safety summary should be based on the ICH CTD requirements as listed below. It should be noted that the draft guidance, "Nonclinical Studies for Development of Pharmaceutical Excipients," is currently being developed by the FDA. Information should be derived using the IPEC safety guide USP general chapter <1074> and should be presented as follows:

1. Brief Summary

2. Safety Pharmacology

3. Single Dose Toxicity

4. ADME and Pharmacokinetics

5. Repeat-Dose Toxicity

    - 1 month
    - 3 month
    - 6 month
    - 9 month
    - etc.

6. Genotoxicity

7. Carcinogenicity

8. Reproductive and Developmental Toxicity

9. Studies in Juvenile Animals

10. Local Tolerance

11. Other Toxicity Studies/Studies to Clarify Special Problems

12. Discussion and Conclusion

13. Tables and Figures (either here or included in text)

The order of presentation given for the Nonclinical Safety summaries should be followed for the preparation of the tables for the protocol summaries/results.

12.6.3 Toxicology Study Reports

Safety Pharmacology studies, ADME, and Pharmacokinetics study reports are reported in separate sections.

A Table of Contents should be provided that lists all the nonclinical safety study reports and gives the location of each study report in the Drug Master File.

The toxicology study reports should be presented in the following order:

1. Single-dose toxicity (in order by species, by route)

2. Repeat-dose toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

3. Genotoxicity (includes supportive toxicokinetics evaluations where appropriate)

    - In vitro
    - In vivo

4. Carcinogenicity (includes supportive toxicokinetics evaluations)

    - Long-term carcinogenicity studies (in order by species; includes range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

    - Short – or medium-term (e.g. transgenic model) studies (includes range-finding studies that cannot appropriately be included under repeat-dose toxicity studies)

5. Reproductive and Developmental Toxicity (includes range-finding studies and supportive toxicokinetics evaluations)

    - Fertility and early embryonic development
    - Embryo-fetal development
    - Prenatal and postnatal embryonic development
    - Prenatal and postnatal development, including maternal function
    - Studies in which the offspring are dosed and/or further evaluated

6. Local Tolerance

7. Other Toxicity Studies (if available)

8. Key Literature References

12.7 Use of Published Safety Data

As previously mentioned in Section 12.2, published Acceptable Daily Intake values are used for the safety assessment of existing excipients with prior food additive approvals or Cosmetic Ingredient Reviews (CIR). New excipients and biotechology-derived excipients are assessed using the guidelines identified in Section 12.1.

Existing excipients either sold alone or in a mixture, may have been marketed first as food additives or cosmetic ingredients. Pharmaceutical applications are typically developed later as the products enter a mature market phase. In this instance, previously published expert reports can be used as the basis for safety assessment. For example, if the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assigned a numerical Acceptable Daily Intake (ADI) of 20 mg/kg/day, then this value can be used for comparison to estimated daily dose calculated in Section 12.2. Another example is review of topical excipients by the CIR. The CIR reviews are comprehensive peer-reviewed publications that provide safe conditions of use of cosmetic ingredients or groups of ingredients.

In the absence of a published ADI for an existing excipient, a margin of safety calculation should be conducted as described below.

12.8 Margin of Safety

The margin of safety is calculated by comparing the estimated daily dose of the excipient (calculated in Section 12.8) with the animal No Observed Adverse Effect Level as follows:

$$\text{Margin of safety} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Estimated daily dose (mg/kg/day)}}$$

A separate margin of safety calculation is conducted on each component of an excipient mixture.

In general, adequate margins of safety are considered to be greater than 100. No significant health effects are predicted with these margins of safety if a complete toxicological database exists. If there is an incomplete toxicological database for an excipient, then it may be necessary to demonstrate a larger margin of safety (1000 or higher). This decision should be made on a case-by-case basis by a qualified toxicologist. The rationale used for this decision should be outlined in the DMF. For excipients that have been previously used as food ingredients, it is not unusual to find

margins of safety that exceed 100,000. However, the margin of safety may vary with each class of biotechnology derived excipients (ICH 1997a).

12.9 Conclusion

The conclusion of this safety assessment should be that the excipient is safe for its intended uses via specific routes of exposure.

It is recommended to re-assess the safety of excipients every few years because certain variables in the safety assessment may change with time, such as:

1. Human exposure to the excipient increases significantly

2. New nonclinical safety data become available for review.

3. A new manufacturing process is used.

4. There is a change in the structure, critical physical properties or impurity profile of the excipient

13. ENVIRONMENTAL ASSESSMENT

The Type IV DMF should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws. If a complete environmental assessment is needed, see 21 CFR Part 25.

14. GLOSSARY

Acceptable Daily Intake (ADI): The amount of a substance that can be ingested daily for an entire lifetime without causing appreciable adverse effects. It is expressed in mg/kg body weight/day.

ADME: Absorption, distribution, metabolism and excretion

Agent: A person appointed by a DMF holder to serve as the contact for the holder.

Batch(Lot): A defined quantity of raw material, intermediate material, packaging components, or final product produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Biotechnology Derived Excipients: Applies to excipients derived from characterized cells through the use of a variety of expression systems including but not limited to bacteria, yeast, insect, plant, and mammalian cells.

Bulk Pharmaceutical Excipient: see "Excipient"

Certificate of Analysis (COA): A document listing the results of testing a representative sample drawn from the batch(lot) to be delivered.

Current Good Manufacturing Practice (cGMP): Requirements for the quality system under which drug products and their ingredients are manufactured. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For the purposes of this guide, the terms GMP and cGMP are equivalent.

Common Technical Document (CTD): The organization of a document recommended by a regulatory body (such as FDA) or conference (ICH).

Co-Processed Materials: An excipient resulting from a manufacturing process where multiple excipients are produced together simultaneously.

Degradants: Materials resulting from the decomposition of the excipient.

Developmental Toxicity: Any adverse effect induced prior to attainment of adult life. It includes effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally.

DMF Holder: The company or individual who has filed a Drug Master File with the United States Food and Drug Administration.

Drug Master File: Detailed information concerning a specific facility, process, or product submitted to the United States Food and Drug Administration intended for incorporation by reference into a new drug application, supplemental new drug application, abbreviated new drug application, investigational new drug application, or biological license application.

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally with excipients, that has been prepared for consumer use and that has undergone all stages of production including packaging and labeling.

Drug Substance: The active ingredient that when combined with excipients become a drug product.

Estimated Daily Dose: see Estimated Daily Intake

Estimated Daily Intake (EDI): The estimated maximum daily intake (I) of the dosage form (tablets per day) and the concentration (C) of the excipient in each dosage form (mg/tablet) divided by the body weight (BW) in kilograms.

$$EDI = \frac{I*C}{BW}$$

Excipient: Excipients are any substances, other than the drug substance, in a drug product which have been appropriately evaluated for safety and are included in a drug delivery

system to either aid the processing of the drug product during its manufacture, protect, support, or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

Expiration Date: The date after which the excipient manufacturer recommends that the excipient should not be used.

FCC: Food Chemical Codex

FEMA: Flavor and Extract Manufacturers Association of the United States

Functionality: The set of performance criteria the excipient is intended to meet.

Genotoxicity, Genetic toxicity: A broad term that refers to any deleterious change in the genetic material regardless of the mechanism by which the change is induced.

GRAS (Generally Recognized as Safe): General recognition of safety based on the views of experts qualified by scientific training and experience to evaluate the safety of a substance for its intended use.

ICH: International Conference on Harmonisation

Identity: The uniqueness of an excipient demonstrated by its physio-chemical properties.

Immediate Container: The receptacle used solely for the transportation of the inert ingredient commodity in bulk or in quantity to manufacturers, packers, processors or distributors.

Impurity: A component of an excipient that is not the intended chemical entity but is present as a consequence of either the raw materials used or the manufacturing process.

Impurity Profile: A description of all of the impurities present in the excipient

Intramuscular (i.m.): A route of administration where the drug product is injected into a muscle.

Intraperitoneal (i.p.): A route of administration where the drug product is injected into the abdominal cavity.

Intravenous (i.v.): A route of administration where the drug product is injected into a vein.

Label: The display of written, printed or graphic matter on the immediate container of the excipient (inactive ingredient) product.

Labeling: All written printed or graphic material accompanying an excipient at any time while it is in-transit to the customer or being held for sale after shipment or delivery to the customer.

Letter of Authorization: A written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another company's submission.

Margin of Safety: An indicator of the magnitude of the difference between an exposed dose to a human population and the highest no observed adverse effect dose determined in test animals.

Mixtures: The physical combining of multiple materials. Excipient mixtures are products resulting from the physical combination of multiple excipients, often through a mixing operation.

Neat Excipient: The pure excipient, containing no other materials.

NOAEL (No-Observed-Adverse-Effect Level): The highest dose of a substance that, in a given toxicity test, causes no biologically significant effects in the exposed test animals.

Non-Official Method (Non-Official Source): An analytical technique not found in compendia or other listings of official analytical methods.

New Excipient: An excipient used for the first time in a drug product or a new route of administration.

Official Method (Official Source): An analytical technique found in a compendia or other listing of official analytical methods.

Oral (p.o): A route of administration where the drug product is taken by mouth.

Packaging Operations: Those manufacturing processes which place the finished excipient into the container and its components designed to hold the excipient for storage and transport to the customers.

PDE (Permissible Daily Exposure): The maximum daily acceptable intake of a substance.

Physical Form: The state, at ambient conditions, in which the excipient is found; solid, liquid or gas.

Purity: The extent to which the excipient is free of foreign materials such as impurities and contaminants.

Quality Assurance/Quality Control: The disciplines with the responsibility and authority to assure the excipient conforms to its specifications and is produced under appropriate GMPs.

Re-evaluation Date: The date beyond which the bulk pharmaceutical excipient should not be used without further appropriate re-examination.

Route of exposure/administration: The method by which the drug product containing the excipient is administered to the patient.

Significant Change: Any change that alters an excipient physical or chemical property from the norm or that is likely to alter the excipient performance in the dosage form.

Specifications: The quality parameters to which the excipient, component, or intermediate must conform and that serve as a basis of quality evaluation.

Stability: The continued conformance of the excipient to its specification.

Starting Materials: Any substances used in the production of an excipient excluding packaging materials.

Statement of Commitment: A declaration by the excipient manufacturer certifying that the DMF is current and that the DMF holder will comply with the statements made there in.

Subcutaneous (s.c.): A route of administration where the drug product is injected beneath the skin.

Typical Usage Level: The quantity of excipient expected to be found in drug products based upon excipient functionality.

USP/NF: The United States Pharmacopeia/National Formulary

15. REFERENCES

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United States Pharmacopeia/National Formulary (USP/NF). General Chapter <1074> Excipient Biological Safety Evaluation Guidelines.

United States Pharmacopeia/National Formulary (USP/NF). General Chapter <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients.

Appendix I
Flavors and Color Additives

A flavor or color additive to be incorporated into a pharmaceutical product generally has a clear, existing regulatory status. Both are subject to the Food and Drug Administration (FDA) pre-market approval requirements, and therefore have already been evaluated for safety unless they are a new flavor or color additive.

Flavor suppliers can provide extensive support to drug and excipient manufacturers seeking to include a flavor in their products. Information related to safety, specifications, and other aspects can be readily provided either by the supplier or by the Flavor and Extract Manufacturers Association of the United States (FEMA). In the case of a new flavoring substance, such substances can be evaluated by the FEMA Expert Panel to determine if they are GRAS. References to the FEMA GRAS evaluations can be included in the DMF to support the safe use of a particular flavor.

FDA provides, by regulation, for the use of a variety of color additives that are either subject to certification (21 CFR Part 74), or exempt from certification (21 CFR Part 73). Only colors which are specifically listed for the intended drug application can be used. References to the applicable section in 21 CFR should be provided in the DMF for all color additives used in the product.

It is necessary to obtain FDA approval before incorporating a new color additive into an excipient product. FDA has a well-defined process for obtaining approval – the color additive petition process described at 21 CFR Part 71. Information related to safety, specifications, manufacture, and use must be provided to FDA. Approvals of new color additives are most commonly sought by color additive manufacturers.