The IPEC-Americas Excipient Master File Guide

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The International Pharmaceutical Excipients Council (IPEC) is developing a global master file guide to meet the need to submit confidential excipient information. The initial focus of the guide is to assist in the improvement of the drug master file system in the United States; however, the intent is to eventually develop a global guide. The format will be coordinated and harmonized with the electronic ICH common technical document for presenting chemistry, manufacturing, and controls as well as safety information.

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Currently the only drug master file (DMF) systems that exist to handle the submission of confidential excipient information to support drug applications are in the United States and Canada. The European Union and Japan do not have such systems for excipients. The International Pharmaceutical Excipients Council (IPEC) is developing a global master file guide to meet the industry's need to submit confidential excipient information. The format for the guide will be coordinated and harmonized with the electronic International Committee on Harmonization (ICH) common technical document (CTD) for presenting chemistry, manufacturing, and controls and safety information (1,2). This system will accelerate the process for submitting information globally because a confidentiality agreement between a DMF holder and a drug application sponsor will not be needed.

Application and scope of the guide

The goal of the master file guide is to allow the DMF holder to submit to regulatory authorities the confidential information that supports marketing authorization applications worldwide. IPEC reviewed various guidances to prepare the draft excipient master file guide (see sidebar "Guidances reviewed by IPEC"). Although the initial focus of the guide is to help improve the DMF system in the United States, the intent is to eventually develop a global guide. IPEC has become aware that Canada is revising its DMF guidelines. Therefore IPEC intends to collaborate with Health Canada on this effort.

In the United States, a Type IV DMF is used for submitting to FDA excipient information that supports an investigational new drug application (IND), a new drug application (NDA), an abbreviated new drug application (ANDA), a biological license application (BLA), a veterinary drug application, another DMF, or an export application. An excipient DMF is not required by law or by FDA regulations; it is submitted solely at the discretion of the holder. It is not approved or disapproved, and FDA maintains the DMF as a confidential document. The DMF contains manufacturing and controls information and technical data that support the safety and quality of the excipient.

The regulatory responsibilities of a DMF holder are cited in 21 *CFR* 314.420. A DMF must include a list of persons authorized to refer to the DMF. If the DMF holder adds, changes, or deletes significant information in the file (except annual updates of authorized users), then the holder shall notify in writ-

ing each person authorized to reference that information. The IPEC *Significant Change Guide for Bulk Pharmaceutical Excipients* establishes uniform considerations for evaluating the significance of changes involving the manufacture of excipients (3).

Transmittal letters to FDA accompany the DMF and instruct FDA about the nature of the submission. The DMF holder should submit in duplicate to FDA a letter of authorization that permits FDA to reference the DMF on behalf of a pharmaceutical sponsor that has included the excipient in its drug application.

In general, the excipient DMF is not used for compendial excipients but more for novel excipients (e.g., new excipients, mixtures, coprocessed materials, and biotech excipients). FDA usually does not review DMFs for compendial excipients unless there is a specific reason to do so. The IPEC guide is for the submission of technical, regulatory, and safety information for the following:

- existing excipients not fully described by monographs (e.g., mixture of excipients)
- new (novel) excipients
- a new route of administration or application for existing excipients
- biopharmaceutical excipients.

About flavors and color additives

The guide includes a section discussing flavors and color additives. Flavors or color additives to be incorporated into a pharmaceutical product generally have clear and existing regulatory status. Both are subject to FDA premarket approval requirements and therefore already have been evaluated for safety unless they are new, novel flavors or color additives.

Information about safety, specifications, and other aspects can be provided readily, either by the flavor supplier or by the Flavor and Extract Manufacturers Association of the United States (FEMA). New, novel flavoring substances can be evaluated by the FEMA expert panel to determine whether the substances are generally recognized as safe (GRAS). References to the FEMA GRAS evaluations can be included in the DMF to support the safe use of a particular flavor.

FDA must approve the use of color additives to be incorporated into drug or excipient products. FDA regulates the use of a variety of color additives that are either subject to certification (21 *CFR* Parts 74 and 82) or exempt from certification (21 *CFR* Part 73). Only colors that are specifically listed for the intended type of drug application can be used. The DMF should include references to the applicable 21 *CFR* section for all color additives used in the product.

FDA approval must be obtained before a new color additive is incorporated into an excipient product. The color-additive petition process described in 21 *CFR* Part 71 is FDA's process for obtaining such approval. Information about safety, specifications, manufacture, and use must be provided to FDA. Approvals of new color additives are most commonly sought by color-additive manufacturers.

Guidances reviewed by IPEC

- ICH common technical document. Module 2 (Quality overall summary) and Module 3 (Quality)
- PhEur certificate of suitability procedure
- FDA guidance for DMFs
- IPEC Europe draft guideline for excipient master files
- FDA MAPP 5015.4 *Chemistry Review for Drug Substance DMFs*
- product master file guidelines for Canada

Sections of IPEC's excipient master file guide

A general description for several selected sections in the guide is presented in this article: description and characterization, method of manufacture, process controls, specifications, and nonclinical safety assessment. The table of contents for the IPEC guide is listed in the sidebar "Table of Contents for the IPEC excipient master file guide."

Description and characterization. Establishment of a meaningful physicochemical profile of a pharmaceutical excipient is fundamental to evaluate its application. Monographs from *USP–NF*, the *Food Chemicals Codex* (*FCC*), or other official sources should be referenced for the characterization of the excipient. However, if new methods of manufacture or new raw materials are used, the excipient's identity should be confirmed and an evaluation of the excipient impurity profile should be conducted (4). Potential isomerism and polymorphism should be investigated when appropriate. Highly complex mixtures from animal and/or botanical sources may require various approaches to characterize their properties.

An excipient that does not have a monograph in *USP–NF*, *FCC*, or other official sources should be thoroughly characterized. Characterization information includes appropriate chemical attributes, information that substantiates the proof of structure, data that establish purity, a physical description of the material, and a detailed description of the analytical procedures that were used. Characterizing biologic excipients can be especially challenging. The physicochemical characterization of biologically derived excipients should include the composition, physical properties, and structure. If the excipient is heterogeneous, then the composition of the mixture should be ascertained.

Facilities, manufacturing, and process controls description. The level of required information about a manufacturing facility depends on a number of factors, including the nature of the manufacturing process and equipment, the intended function and route of administration of the pharmaceutical excipient, and the nature of any other product that is manufactured at the facility. The facility should be suitably constructed to ensure that the excipient is manufactured and packaged to the required quality. General design information for the facility should be included.

Laboratory testing is considered part of the manufacturing process. Information about all testing facilities should be provided, including the general laboratory capabilities at each site. In addition, companies should list the address of each laboratory site that will conduct product-release tests if these sites are different from the laboratory for other manufacturing activities.

Excipient companies should provide a summary of major corporate organizational elements — including key quality control and quality assurance positions, responsibilities, and re-

porting structures — at both the manufacturing site and at corporate headquarters. In addition, companies should list the origin of all starting materials if information about the origin is reasonably relevant. A description of the starting-material processes that may inactivate potential pathogens and/or contaminants can be provided.

Excipient companies should describe the manufacturing process and the raw materials used in the manufacture of the excipient. The information should be written as well as presented in a process-flow diagram to facilitate understanding of the details. All the key processing steps, storage, and distribution of the product are important parts of the manufacturing process.

Companies should describe the manufacturing process and material controls and the location of the controls. Criteria and results that determine the protection and safety of the containers, closures, and components as well as labeling-system controls also should be described.

Batch analysis and certificate of analysis. Information about representative batch analysis should be provided on the basis of defined product specifications. A sample certificate of analysis (COA) should be included. The COA should be generated from batch record data or from a final batch. The source of the data for the COA should be referenced. IPEC's *Certificate of Analysis Guide* is an excellent reference for determining the design and content of the COA (5).

Specifications. The excipient should be identified and characterized by its specifications. The 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.

If the excipient is produced in conformance with a monograph, then the excipient specifications should include all monograph test requirements. In addition, the test methods used by the manufacturer should be validated to demonstrate that they provide results comparable with those of the monograph test method. The specifications for an excipient that is not the subject of a compendial monograph generally should include the following: a description, identification, and information about assay, impurities, water content, physicochemical tests, and microbial limits. For excipient mixtures, incorporating specifications for the individual components may be more important than doing so for the excipient mixture because these specifications are more related to the safety assessment.

Nonclinical safety assessment. Companies should provide the name of the excipient and information about its toxicologically relevant impurities. In the case of an excipient mixture, components and their percentages should be listed. Where applicable, it may be important to demonstrate that chemical interactions between the components have been minimized.

In the United States, the IPEC-Americas safety committee has published a guideline for the safety assessment of new excipients (6), which has been published as General Chapter ⟨1074⟩ in *USP 24–NF 19* (7). 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 (8). These safety assessment guidelines can be used to determine the extent of the toxicology testing program for an excipient.

Companies should summarize the history of the use and status of the excipient or its constituent substances. This summary should include information such as the current use in food or

Table of Contents for the IPEC excipient master file guide

other consumable products, current regulatory status in the country of filing (such as GRAS status) as well as in 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.

Examples of new uses for an existing excipient include a new route of exposure (e.g., from dermal use to oral use) or increased use level by the same route of exposure. The administration of existing excipients to special populations (e.g., children and immunocompromised individuals) also should be taken into account in a safety assessment. The safety assessment of biotechnology-derived excipients (9) and existing excipients not fully described by monographs is undertaken on a case-by-case basis through discussions with the regulatory agency.

On the basis of current safety data, the general route of exposure of the excipient and its maximum usage level in a dosage form should be stated. Every effort should be made to calculate the estimated maximum daily dose of the excipient. Exposure assessment of excipients by various routes of administration has been described previously in the literature (10). For excipient mixtures, the estimated daily dose can be determined by calculating the overall estimated daily dose and then multiplying this value by the percentage of each component. The estimated maximum daily dose for each component is used for safety assessment.

Companies should include an assessment of the impurities and degradants present in the excipient and describe 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 DMF documentation. The ICH guideline about limits for impurities and residual solvents should be applied when the excipient is being developed (11).

The margin of safety can be calculated by comparing the estimated daily dose of the excipient with the animal no observed adverse effect level. A separate margin of safety calculation can be conducted for each component of an excipient mixture. The conclusion of the safety assessment should be provided.

Information presentation. The IPEC guide discusses the arrangement of information for an ICH CTD format (1). Relevant areas include overviews, tabulated summaries, toxicology summaries, order of presentation of information within sections, routes of administration, toxicology study reports, and published safety data.

Current status

IPEC presented the draft guide for review to US and Canadian regulatory authorities. The draft guide was presented at a public meeting at a DMF workshop sponsored by Michigan State University in March 2002. In addition, the draft guide was presented at the FDA Office of Pharmaceutical Science, Pharmaceutical Trade Association meeting in April 2002. FDA agreed to provide comments to IPEC for the guide.

IPEC committee members

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The current European DMF system is structured with an open and a closed section. Recently the European Agency for the Evaluation of Medicinal Products issued its *Draft Note for Guidance on the European Drug Master File System.* The draft document proposes to extend the DMF system to include novel excipients. IPEC submitted a statement that supports a legislative change to include novel excipients in the guidance. IPEC will submit detailed comments for the guidance by the required date of 31 August 2002 and will provide a copy of the IPEC excipient master file guide for comment.

The Ministry of Health, Labor, and Welfare (MHLW) in Japan is considering the introduction of a DMF concept into the Japanese drug administration. The MHLW also is planning a substantial amendment to the Pharmaceutical Affairs Law. The timing of a DMF concept in Japan currently is under review. The Japanese Pharmaceutical Excipients Council will provide comments on the IPEC-Americas excipient master file guide.

Conclusion

IPEC has been concerned for some time that no regulatory mechanism exists in which a new excipient can be assessed centrally for safety and quality. Therefore, the pharmaceutical industry has been reluctant to use new excipients, which in turn could prevent the advancement of pharmaceutical technology.

The implementation of a global DMF system to handle confidential information for excipients may support efforts for an independent acknowledgement and review system for new excipients. New excipients could be evaluated with a base set of data for general acceptance similar to the programs established by the Flavor and Extract Manufacturers Association for flavor ingredients and the Cosmetic Ingredient Review for cosmetic ingredients. However, the use of a new excipient still would be subject to final approval as part of a drug product, and specific-use information would be supplied with the drug product submission.

IPEC's approach to initiate global acceptance of the guide will be to incorporate the guide into an ICH process. The IPEC guide can serve as the framework for the submission of information in a CTD format. Data would be given confidentially to regulatory agencies to support the safety and quality of the excipient.

A copy of the IPEC-Americas excipient master file guide, when available, can be obtained by contacting Alan Mercill at IPEC-

Americas, 1655 N. Fort Myer Dr., Suite 700, Arlington, VA 22209, tel. 703.875.2127, fax 703.525.5157, ipecamer@aol.com, or through the IPEC-Americas Web site at www. ipecamericas.org.

Acknowledgments

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