OFFICE OF NEW DRUGS

Management of the PTCC Inactive Ingredients Subcommittee

CONTENTS

PURPOSE This MAPP describes the:

- Roles and responsibilities of the PTCC Inactive Ingredients Subcommittee
- Structure and function of the subcommittee
- Procedures for designating members to serve on the subcommittee
- Types of members that will be designated to serve on the subcommittee
- Responsibilities of those designated to serve on the subcommittee
- Subcommittee procedures

BACKGROUND

- CDER pharmacology subcommittees have been established to develop regulatory guidance for use by sponsors and applicants, to apply current scientific knowledge to emerging technical problems, and to aid in the review process. The PTCC Inactive Ingredients Subcommittee was established to assess the safety of inactive ingredients of drug products. The subcommittee consists of FDA pharmacologists, toxicologists, and other biomedical scientists who are interested in inactive ingredients that are defined as substances that have no therapeutic value. Inactive ingredients may be deliberately added to a drug product or may be unintentional contaminants. Examples of intentional inactive ingredients include excipients, wetting agents, solvents, emulsifiers, preservatives, and coloring agents. Other inactive ingredients, those that are not intended to be present in a given drug product and are commonly referred to as impurities, include degradation products, by-products of synthesis, compounds leached or extracted from a container, residual solvents, and extraneous contaminants. It should be emphasized that although these *inactive* ingredients have no direct therapeutic value, they are potential toxicants. Therefore, it is important to perform a safety assessment on inactive ingredients of drug products, and to establish maximum permissible limits for these compounds. Actions of the PTCC Inactive

Ingredients Subcommittee that pertain to impurities should reflect familiarity with relevant ICH guidances (see References section below).

REFERENCES

- ICH Q3A Impurities in New Drug Substances, FDA guidance for industry, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.
- ICH Q3B(R) Impurities in New Drug Products, FDA guidance for industry, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.
- ICH Q3C Impurities: Residual Solvents, FDA guidance for industry, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.
- Management of CDER Pharmacology/Toxicology Coordinating Committee, charter of the PTCC, CDER MAPP 7400.1, available on the Internet at http://www.fda.gov/cder/mapp.htm.
- Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, forthcoming FDA guidance for industry.
- Osterberg, RE and N See, 2003, Toxicity of Excipients--A Food and Drug Administration Perspective, Int J Toxicol, 22:377-380.

ABBREVIATIONS

- CDER - Center for Drug Evaluation and Research
- FDA - Food and Drug Administration
- ICH - International Conference on Harmonization
- IND - investigational new drug application
- MAPP – Manual of Policies and Procedures
- NDA - new drug application
- PTCC - Pharmacology and Toxicology Coordinating Committee

ORGANIZATION

Oversight

- The PTCC provides oversight for the PTCC Inactive Ingredients Subcommittee.

Membership

- Expertise and interest in the toxicology of inactive ingredients and the ability to actively participate in committee functions are the basis for an invitation to

membership on the PTCC Inactive Ingredients Subcommittee. Three types of members may serve on the committee:

1. **Chairperson and Co-Chairperson** – The Chairperson will be a reviewer who is a pharmacologist, toxicologist, or other biomedical scientist; the Co-Chairperson will be a supervisor from any of these disciplines from within CDER. These individuals will be selected by the PTCC. Selection of candidates will be based upon expertise, experience, and interest in the toxicology of inactive ingredients, and on organizational and managerial skills. The nominal duration of the term of office of each Chairperson and Co-Chairperson will be 2 years, although the PTCC may modify the length of a given term.

2. **Core members** will be pharmacologists, toxicologists, and other biomedical scientists in CDER and will be selected from a list of volunteers requesting membership. The subcommittee will usually consist of approximately six individuals (including the Co-Chairs). In general, for the PTCC Inactive Ingredients Subcommittee to benefit from as broad of a knowledge base as possible, each member of the committee will be selected from a different review division. Core memberships usually last for 2 years, although the subcommittee or the PTCC may modify the length of a given term.

3. **Ad Hoc members** will be recognized FDA experts (from inside or outside CDER) who are asked to serve the PTCC Inactive Ingredients Subcommittee in a limited capacity (e.g., provide advice on special projects, serve on working groups, comment on policy initiatives). Extension of ad hoc membership will require the approval of the PTCC. Ad hoc members will not be eligible to vote on committee motions.

- Additional CDER members may be added to the core committee membership when the membership drops below six persons. Membership is reviewed by the PTCC either annually or when changes in membership occur (e.g., due to a resignation). A member who does not attend three consecutive meetings may be removed from the committee unless extenuating circumstances, such as illness or a temporary increase in work load, are reported to the Chairperson or Co-Chairperson.

RESPONSIBILITIES

Responsibilities of the committee, as well as those of the Chairperson, Co-Chairperson, and core members, are outlined below.

The PTCC Inactive Ingredients Subcommittee will:

- Serve as a source of advice and assistance to the PTCC and CDER on issues that pertain to the toxicology of inactive ingredients. Requests for advice or assistance should go through the Pharmacology staff.

- Upon request by the PTCC or a CDER division, review the toxicology data available for a given inactive ingredient. If appropriate, the subcommittee will make a recommendation regarding an acceptable level of exposure to the compound in question. Such action by the committee may result in a recommendation concerning

the maximum safe level of that inactive ingredient in a particular drug product. Committee recommendations will not be binding but will be sent to a review division for consideration in the review process. As appropriate, and following concurrence by the PTCC, recommendations of the PTCC Inactive Ingredients Subcommittee that concern maximum acceptable levels of impurities will be made available to the review chemists of CDER for implementation by CDER review divisions. The subcommittee may refrain from making a recommendation concerning acceptable exposure if it concludes that adequate data are not available. In such cases, it may recommend toxicology studies that either a corporate sponsor or an appropriate governmental agency could perform to generate the necessary data.

- Upon request and at the discretion of the PTCC and the PTCC Inactive Ingredients Subcommittee, assist corporations in characterizing inactive ingredients through review of toxicology data that have been submitted to a Drug Master File (DMF) or to the committee. Following the review, the subcommittee may recommend additional studies that would further develop the safety profile of the inactive ingredient. With concurrence of the PTCC, the subcommittee may incorporate a written review into the DMF; the review could subsequently be used by review divisions as desired. The subcommittee will not interject itself into matters that pertain solely to an active IND or NDA unless requested to do so by the review division to which the application was assigned.

- Generate guidance documents that concern inactive ingredients. The guidance documents would require ratification by the PTCC and other groups or individuals, as appropriate, before implementation.

- As appropriate and upon request by either a review division or the Associate Director for Pharmacology, attempt to resolve differences between a review division and a regulated organization that relate to characterization of inactive ingredients. For example, if a review division believed that specific additional toxicology data were necessary to adequately characterize an excipient or impurity but the sponsor of the associated application felt the requests were excessive, the matter could be referred to the PTCC Inactive Ingredients Subcommittee for comment. Recommendations generated by the subcommittee would be reported to the PTCC and sent to the review division.

- Document and keep records of committee recommendations, decisions, and actions.

The Chairperson, Co-Chairperson, and/or their Designee will:

- Have the same responsibilities as those listed for core members (see subsection below). Also, the Chairperson (or a designee) will schedule and organize meetings, distribute documents, maintain files of committee activities, write minutes, and ensure accuracy of committee documents. The Co-Chairperson may call and run meetings in the absence of the Chairperson.

- Coordinate the efforts of the PTCC Inactive Ingredients Subcommittee and ad hoc working groups and maintain a list of the major tasks the committee is undertaking, including projected completion dates and the current status of each project. The

Chairperson or Co-Chairperson will provide to the PTCC, upon request, an updated list of committee activities, a summary of achievements since the last report to the PTCC, a projection of future activities, and a list of issues for which PTCC input is needed. The Co-Chairperson will assist the Chairperson as needed and serve as a liaison between the PTCC and the PTCC Inactive Ingredients Subcommittee, regularly updating both groups.

The Core Members will:

- Regularly attend committee meetings and review materials before the meetings. Members are responsible for maintaining familiarity with relevant scientific and regulatory literature or guidances. Members will be expected to participate in committee activities (e.g., accepting an assignment to review the toxicology data associated with an inactive ingredient and submitting a written report to the committee in a timely manner).

PROCEDURES

- Meetings of the PTCC Inactive Ingredients Subcommittee will be scheduled as needed.

- The Chairperson, the Co-Chairperson, and the core members of the committee are eligible to vote on an equal basis on motions that are raised at a meeting.

- Motions can be passed by a majority vote of the members that are present at a meeting. However, if circumstances dictate a rapid decision, matters can be acted upon in the absence of an official meeting through agreement of the Chairperson and the Co-Chairperson.

- All formal actions of the committee will be documented in written reports that include a description of the issues that were dealt with, major points that were raised, the outcome of any vote by the committee, and detailed information about actions that were taken.

- Reports will be the responsibility of the Chairperson of the committee.

EFFECTIVE DATE

This MAPP is effective upon date of publication.