International Pharmaceutical Excipients Council
Of The Americas

December 30, 2002

Documents Management Branch
HFA – 305
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 02D-0389 – Draft Guidance for Industry: Nonclinical Studies for Development of Pharmaceutical Excipients

Dear Sirs:

The following comments are submitted on behalf of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). IPEC-Americas is a regional pharmaceutical industry trade association headquartered in Arlington, Virginia. Many of its member companies are U.S. based and manufacture either finished drug products or components used in such products for various purposes, and therefore are affected by the subject guidance. IPEC-Americas appreciates the opportunity to provide these comments. Individual member companies may also elect to do so separately.

General Comments

1. IPEC-Americas applauds and generally supports the agency's effort to produce and publish this important guidance. In essence, this guidance is the culmination of work begun years ago by Ralph Shangraw and others that has led to a greater understanding of the different roles excipients can play in the pharmaceutical manufacturing process and in drug delivery itself.

2. We believe it is important to note that in addition to agency reviewers and industry drug formulators, this guidance will also be important to excipient producers. Many such companies are engaged in the development of new materials for use in pharmaceuticals, as well as for new uses of older materials. As the agency is aware, this has become more frequent in recent years and has resulted in a number of significant therapeutic advances.

   A recent case in point involves development of a patented cyclodextrin delivery technology that has been determined to be suitable for use in at least two FDA approved drugs in 2002. Initial safety and other supportive data was compiled by the developer of the delivery system, using testing guidance that predated the agency's and which was developed by an IPEC-Americas committee. This data was added to the

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company's excipient master file that was then utilized by another IPEC member company to support NDA's that included the cyclodexterin technology. It is recommended therefore, that the Background section of the Guidance be amended to include the role that excipient manufacturers also provide in the development of new pharmaceutical excipients.

3. With respect to Section III, we agree there is a long history concerning the use of the MTD or MFD as the upper dose limit for multiple dose toxicology studies. However, in most instances where this approach is used, the final clinical exposure is not well defined. Where the exposure is known, it is not unusual for an appropriate multiple of the highest clinical exposure to be used as the upper limit in the toxicology studies. It is recommended that a multiple of no less than 25 X over the intended maximum exposure (based on the ICH guidances S1C and S1C R) be considered as an alternative to the use of an MTD or MFD. Drug product manufacturers having knowledge of the anticipated exposure may find this useful, while excipient manufacturers, either not knowing the anticipated exposure or aiming at multiple uses for an excipient, may find using the MTD or MFD more appropriate. Either approach should provide appropriate safety to a patient.

   IPEC-Americas also suggests that the Guidance would benefit from having some written attention directed to endocrine disruption. The use of a material as a pharmaceutical excipient generally is a very small part of the use of the product. Once a material has been considered safe for use as a component in a drug product, no additional safety work will probably be performed. Therefore, either some emphasis should be placed on the potential for this toxicity or an appropriate reference to another agency should be provided.

Specific Comments

1. Lines 59 – 62, page 2:

   The Draft Guidance states that it may be important for the safety database associated with a qualified excipient to be brought up to current standards as stated in the guidance. Since the available data for many common excipients is likely to be lacking, would industry then be liable for filling in data gaps on excipients with extensive human experience?

2. Lines 233 – 249, page 6:

   The weight of evidence approach will be important if an excipient used in an acute dosage is proposed for a new chronic dose regime.

3. Line 110, page 3:

   "Excipients" is misspelled

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4. Line 122, page 3 (suggested correction):

   S7 guidance includes S7A and S7B

5. Line 269, page 7:

   Repeat dose pivotal studies in non-rodents are defined by the ICH M3 guideline. IPEC-Americas believes that the duration of the nonrodent 9-month repeat dose should be sufficient and should not be extended to one year

6. Line 277, page 7:

   We believe that photosafety testing should be conducted if such testing is applicable to a particular situation at hand.

We appreciate the opportunity to provide these comments and hope they are helpful to the agency.

Sincerely,

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Chairman

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