International Pharmaceutical Excipients Council
Of The Americas

June 24, 2003

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

RE: Docket No. 02D-0526 – Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information

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. This guidance is parallel to the efforts of IPEC-Americas to ensure the safety of excipients used in pharmaceutical products. It 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 innovation has become more frequent in recent years and has resulted in a number of significant therapeutic advances.

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3. Our major comments concern the need for explicit registration of methods used for testing pharmacopoeial excipients. We, of course, agree that the specifications applied to excipients must be consistent with those of the pharmacopoeia, and that methods used must be appropriate to demonstrate compliance. The question we wish the Food and Drug Administration (FDA) to consider more carefully is the amount of paperwork necessary to ensure appropriate control of those excipients.

   Excipients are an important part of most formulations, and in many cases the quantity of excipients is much greater than the active substance. Clearly, excipients must be controlled to ensure the quality of the pharmaceutical product and patient safety. However, excipients differ from most active substances and finished products in that excipients are often used in multiple products.

   Because of this fundamental characteristic, testing of a single excipient has a potential to impact many New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA). Moreover, once initial product submissions are made, maintenance of excipient commitments in multiple NDAs/ANDAs becomes a significant burden for both manufacturers and the FDA.

4. The language used in sections P.4 through P.4.4 would require manufacturers to specify each method used for routine testing of excipients, unless the method is exactly that of the pharmacopoeia. Two situations commonly occur which are impacted by this requirement:

   First, methods are used which have been demonstrated to be equivalent or superior to those in the pharmacopoeia. Often a manufacturer has methods used internally that are shown to produce equivalent results to those in the pharmacopoeia. Also, many manufacturers must meet global requirements and seek to eliminate redundant testing of the same property (e.g., European Pharmacopoeia (PhEur), United States Pharmacopeia – National Formulary (USP-NF), and Japanese Pharmacopoeia (JP) Heavy Metals tests) by selecting a single method shown to be capable of ensuring compliance with all the requirements.

   Second, excipient testing is performed by the supplier and accepted on Certificate Of Analysis (COA). Suppliers are generally expected to perform testing to demonstrate compliance with pharmacopoeia requirements, and pharmaceutical manufacturers often accept the supplier results on COA. With proper auditing of supplier processes and lab capability, this practice ensures compliance.

   In each of the cases above, the pharmaceutical manufacturer must have systems in place to ensure compliance. However, even with appropriate internal controls, the regulatory hurdles in implementing and maintaining such systems are significant.

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5. Because a particular excipient may be used in many products, submissions of the routine excipient-testing program would be required in many product registrations. If the testing program were to be changed, for example, to reflect acceptance on supplier COAs or adoption of tests shown to meet multiple pharmacopoeias, each of these product registrations would have to be changed. Also note that pharmacopoeia change frequently, so that testing regimes must also be amended to conform.

6. In summary, this guidance would drive industry to adopt full monograph testing for each excipient using the exact methods specified in the USP-NF or Homeopathic Pharmacopoeia. The draft guidance presents barriers for companies utilizing alternative methods (e.g. PhEur, or JP), or vendor qualification strategies using audits or reduced testing protocols that eliminate redundant excipient tests. As written, the draft guidance creates a paperwork burden that would eliminate existing vendor qualification programs.

Specific Comments

(Guidance Citations are in Times New Roman font, and comments are in Arial)

Line #s, page #	Guidance Citations with comments
Lines 981 – 987, page 27	"Compendial–Non-novel Excipients: When a compendial excipient is tested according to the monograph standard with no additional testing and the applicant intends to perform full testing on each batch received, the excipient (e.g. Sodium Chloride, USP) can be listed under P.4 with no detailed information provided in P.4.1 to P.4.4. The implication is that the applicant will not be able to use vendor qualification to accept excipients via COA without providing additional information in the application. On the other hand, the USP General Notices state that application of every analytical procedure is not needed to meet compendial requirements. In addition, 21 CFR 211 states "In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one identity test is conducted by the manufacturer." In such cases, the manufacturer establishes the reliability of the supplier's test results through validation at appropriate intervals. It is not reasonable to require the pharmaceutical manufacturer to commit to fully test all excipient lots.
Lines 1022 – 1024 and Footnote 27, page 28	" In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's COA." The drug manufacturer does not normally know at the time a submission is filed which tests will be accepted from the vendor's COA. At submission, the manufacturer may have limited experience with some of the excipients or suppliers. Because there is limited experience with new excipients, or new suppliers, an excipient from supplier 1 might be accepted on a COA, but the same excipient from supplier 2 might require full testing. Therefore, a reduced testing program by the drug product manufacturer would only be implemented well after submission of the NDA. Deletion of the requirement and footnote is requested.

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Line #s, page #	Guidance Citations with comments
Lines 1026 – 130, page 28	"However when there are specific concerns relating to an excipient, testing in addition to an identity test would be warranted." Revise the statement to read "...testing in addition to an identity test may be warranted." And "For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities..." This is an example where basic GMPs were not used. The impact of this tragedy is great and cannot be ignored, but other tools are available to ensure excipient and excipient supply chain safety. When excipient suppliers and users apply appropriate GMPs the excipient supply chain is made reliable. For glycerol, the USP monograph includes specific testing for diethylene glycol, so the reference to this specific 'additional testing' is unnecessary.
Lines 1032 – 1035, page 28	"Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph and full monograph testing will be performed on each batch of excipient" Excipient Quality is not improved by full monograph testing. If other internal testing and audits have confirmed excipient supplier data, then supplier data can be accepted. See Lines 981 – 987 for similar comments.
Lines 1035 – 1038, page 28	"When the specification for a compendial excipient differs from the compendial monograph, (e.g., additional tests, tighter acceptance criteria than in the monograph, different analytical procedures) or test results will be accepted from the excipient manufacturer's COA, the in-house specification should be provided." See Lines 981 – 987 for similar comments.
Lines 1038 – 1041, page 28	"If the specification for an excipient is based on a compendium other than an official compendium, the excipient should still conform to the monograph in an official compendium, if there is such a monograph" The "official compendium" should clearly state USP-NF and Homeopathic Pharmacopoeia. This section should refer to PhEur and JP, specifically because there is much current effort to bring USP, PhEur and JP into a greater degree of agreement. There is a difference between conforming to a monograph and to a compendia. Focus on the monograph eliminates General Chapters, and GMPs that are in place to ensure excipient safety.
Lines 1043 –1046, page 29	"However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive." Sentence deletion is requested, because the phrase is duplication of compendia requirements.

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Lines 1089 - 1092, page 30	"A COA from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4." This requirement duplicates GMP requirements for confirmatory testing. Please delete the sentence.
Lines 1092 – 1094, page 30	"Test results should be expressed numerically or qualitatively (e.g. clear, colorless solution), as appropriate. Use of terms such as conforms or meets specification is discouraged." If the material must pass the compendia test, then there is little point in putting in different qualitative text such as "does not form precipitate" or "violet-blue color" from the method onto the COA. For this type of compendial requirement, it either meets the specification or it doesn't. Therefore, on the COA, for compendial tests, it is sufficient to report the test result as "pass". For non-compendial methods, there may be value to reporting the results numerically or qualitatively since the expected results of non-compendial tests may not be obvious to a reader. Please delete "Use of terms such as conforms or meets specification is discouraged."

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

Sincerely,

R. Christian Moreton, Ph.D.
Chairman

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