



*International Pharmaceutical Excipients Council
Of The Americas*

R. Christian Moreton, Ph.D.
Chairman

August 17, 2004

Dockets Management Branch [HFA-305],
Food and Drug Administration,
5630 Fishers Lane, room 1061
Rockville, MD 20852

**Re: Docket # 1999N-0193 Guidance for Industry;
Changes to an Approved NDA or ANDA (69 FR 18728-18767, April 8, 2004)**

Dear Sirs:

The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) is an organization representing both makers and users of pharmaceutical excipients. Excipients are used in almost all approved drug products in some way and are essential to the performance of the product. Most excipients used in pharmaceutical products for sale in the United States are manufactured to comply with the standards of the United States Pharmacopeia/National Formulary (USP/NF) and are used in multiple products. In this they are very different to active pharmaceutical ingredients (APIs) since they are used in many different drug products, and with very different functional characteristics depending on the particular type of formulation.

IPEC-Americas is concerned that some parts of the revision to 21 CFR 314.70 increases the regulatory burden without benefit to the patient, the FDA or industry with respect to excipients. The revision as written has the potential to affect all compendial ingredients, whether excipient or API. A major concern of IPEC-Americas is the revised requirement that changes to an excipient specification involving "relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements" now requires a supplemental filing (CBE-30) rather than notification via an Annual Update letter as was previously the case.

There is an active program of global harmonization of excipient monographs through the Pharmacopeial Discussion Group (and with the active assistance of IPEC Americas, IPEC Europe and JPEC [TriPEC]). The USP has also stated its intention to bring its monographs and General Chapters up to date. There is also the FDA's own PAT initiative. IPEC-Americas believes that all three of these important, necessary initiatives could be compromised by the changed requirement for a CBE-30 supplement for certain changes to a USP/NF monograph for an excipient.

A quick review of several key excipients using the redacted 1996 version of the Inactive Ingredient Guide (IIG) revealed the following data for numbers of products containing a particular excipient. (The totals are for all routes and types of administration since a monograph change will probably affect all grades of an excipient and all products containing it.)

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Microcrystalline cellulose (all grades)	1650+
Lactose (all grades)	1950+
Titanium dioxide	1050+
Magnesium stearate	2200+
Povidone (all grades)	about 690
Hydroxypropyl methyl cellulose (all grades)	about 130

In the cases of lactose, titanium dioxide and hydroxypropyl methyl cellulose, it is also well known that these materials are frequently components of mixed excipients, e.g. film coating formulations, and this would increase the number of supplements even further.

The 1996 IIG was used because it includes information on the number of products. We realize that the information is out of date, but the numbers are at least an indication of the size of the problem since the number of products has probably increased rather than declined in the last 8 years. We also know that the excipients listed, with the exception of lactose, are the subject of on-going harmonization efforts. If a change were to be announced in the Pharmacopeial Forum, typically there is about one month between the release of the Interim Revision Announcement and its implementation. According to the revised requirement, all companies with products containing an excipient whose monograph is changed in certain ways would be required to file a CBE-30 supplement immediately to maintain production, etc. Could the FDA cope with the filing of 130 (and probably many more) CBE-30 supplements for hydroxypropyl methyl cellulose, let alone the 2200+ supplements if the magnesium stearate monograph were changed in such a way? Could industry cope with the intense workload necessary to prepare the requisite supplements? This is doubtful, and companies would find themselves almost immediately out of compliance.

IPEC-Americas wrote to the Agency to question the proposals in an earlier submission to the docket (letter dated August 27th, 1999 - attached). We are at a loss to understand why our concerns appear to have been discounted, and IPEC-Americas wishes to re-emphasize our belief that the changed rule is overly burdensome as it affects excipients.

During the rulemaking process, FDA must consider the economic impact of the new regulation. The Regulatory Flexibility Act, 5 U.S.C. § 601 – 612 and the Unfunded Mandates Reform Act, Public Law 104-4, along with Executive Order 12866 provide that agencies must determine if the new regulation will meet certain cost thresholds, and if so, assess the cost and benefits of alternatives to the regulation. The thresholds in question are 1) if the aggregate cost of the regulation to industry and government exceeds \$100 million dollars, or 2) if the regulation will have “a significant economic impact on a substantial number of small entities.”

For the new 21 CFR 314.70, FDA has made the determination (found at 69 FD 18759, April 8, 2004) that the costs associated with the new regulation do not exceed the above thresholds. However, it is evident from the Federal Register notice, that the Agency did not consider the potential impact of the regulation should it be read in such a way as to require excipient users to file CBE-30 supplements for changes made to excipient specifications to comply with compendial changes.

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The revision of 21 CFR 314.70 also seems to IPEC-Americas to be at odds with the intentions of Congress in the FDAMA legislation, since the changes bring an increased regulatory burden with no apparent increased safeguard of the public health. The changed rule also appears to be contrary to the sentiments expressed by senior representatives of the Office of New Drug Chemistry and the Office of Generic Drugs at the recent meeting of the Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science (July 20 – 21, 2004, Rockville, MD). The point was made several times by speakers from both Offices that the Agency would like to reduce the number of supplements it receives. It is IPEC-Americas' position that the changed rule is likely to markedly increase the number of supplements received by both Offices.

IPEC-Americas is further concerned that the CBE-30 requirement for the notification of certain changes to pharmaceutical excipient compendial monographs and specifications may have the unintended effect of stifling the harmonization of excipient monographs, as well as the USP/NF monograph modernization program.

The Agency has recently launched its PAT initiative. A key premise of this initiative is that well understood starting materials (excipients and APIs) and well-engineered processes will produce more consistent (less variable) products. Obviously a key part is the excipients in the formulation. IPEC-Americas is concerned that with the introduction of the CBE-30 requirement, even if tests are discovered or developed that give better information on the potential performance of an excipient, there may be a reluctance to introduce them via the USP/NF because of the potential burden of filing the CBE-30 supplements.

IPEC-Americas wishes to reemphasize its view that the revised requirement for CBE-30 supplements for changes in excipient specifications due to changes in the compendial monograph is over burdensome to industry, does not add to the safety of the public health, and will overburden the FDA's own resources to such an extent that the system may become unworkable.

We therefore request that the Agency consider an exemption for pharmaceutical excipients from the revised requirements of 21 CFR 314.70 that will allow the reporting of changes in excipient specifications due to changes in the pharmacopeial monograph to continue to be reported in the Annual Update letter.

Yours faithfully,



R. Christopher Moreton
Chairman, IPEC-Americas

Enclosure