



31 July, 2015

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-D-1659: Draft Guidance on Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products

Dear Sir/Madam:

ISPE appreciates the opportunity to comment on this draft guidance. In general, this represents an important initiative by FDA to further implement the vision first established by the cGMP 21st Century Initiative providing for “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight” (Janet Woodcock, M.D. Pharmaceutical Quality Assessment Workshop October 5, 2005).

Specifically, ISPE would like to highlight the following areas and make certain recommendations to better facilitate this overall goal, promote continual improvement, and provide industry with the primary responsibility for development, manufacturing, and continual improvement of the processes and products produced. FDA and industry have a shared responsibility to ensure a supply of quality products to patients with the realization that patients exist in a global setting. Making and reporting CMC changes can require multiple approvals from health authorities worldwide which can discourage or delay continual improvement efforts. It also should be noted that in many instances, regulatory consequences -- e.g., the issuance of 483 observations -- can be avoided if changes for continual improvements were not delayed or discouraged due to the burden of filing post approval changes.

- Overall, the guidance is a positive step forward in lessening the burden of filing post approval changes. Provisions exist in the regulatory framework of 21CFR 210 and 211 cGMP and ICH Q7 to manage the manufacturing of pharmaceuticals over the product lifecycle. This has been amplified in ICH Q10, Pharmaceutical Quality Systems (PQS). It also is important to recognize that many products under the US regulatory system are successfully managed under 21CFR 210 and 211, e.g., OTC monograph products.
- In general, the document recognizes process validation not to be an established condition, however; this is somewhat in conflict with equipment settings and ranges that are considered established conditions (Ref. CTD Section 3.2.S.2.2). Parameters, equipment settings, unless determined to be critical to quality attributes or well established, e.g., sterilization parameters,

should generally not be considered established conditions, or the applicant should at least be able to provide such justification in accord with Quality Risk Management principles, ICH Q9. This same principle holds true for footnote 16, "...providing supporting elements (e.g. validation data, batch analysis) ..."

- There are a number of references to control strategy in the document. This term as defined in ICH Q10 reflects the current knowledge of the product and process. However, in a number of places in the guidance, e.g., footnote 13, P 6 it states, "... but if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory submission..." It should be made clear that this is not necessarily becoming an established condition but supportive information. Also to be noted, the regulation points out also that a Master Record primarily be submitted and a batch record in the alternative.
- Specific reference at line 166 to maintenance for chemometric and/or multivariate models appears to be in direct conflict with ICH Q8R, Section 2.6 which clearly states this should be maintained under the PQS.

In conclusion, while not specifically mentioned in the draft guidance, FDA is represented in the Expert Working Group, ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. It is important that FDA and the various international industry groups also agree on the concepts at that forum, as it is only through regulatory convergence can the global pharmaceutical industry benefit and advance quality in the lifecycle management of products. ISPE stands ready to assist through the technical and regulatory members it represents to provide input to FDA and international competent authorities through its educational conferences and workshops globally.

Please contact ISPE Director of Regulatory Affairs, Carol Winfield, for any follow up questions or information.

Sincerely,

John Bournas, ISPE President and CEO