Abbott

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September 17, 2010

RE: **Docket No. FDA-2010-D-0283**
Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports

Dear Sir or Madam:

Abbott Laboratories is a global, broad-based health care company devoted to discovering new medicines, new technologies and new ways to manage health. Our products span the continuum of care, from nutritional products and laboratory diagnostics through medical devices and pharmaceutical therapies.

We are pleased to provide the following comments regarding the **Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports** published in the Federal Register on June 25, 2010 at Vol. 75, No. 122, Pages 36421-36423.

General Comments:

1. There are multiple final FDA guidances that provide recommendations on how the Agency wishes to be notified of post approval CMC changes[1]. Further, some of the changes

[1] "Changes to an Approved NDA or ANDA" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf)

"Changes to an Approved NDA or ANDA: Questions and Answers" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122871.pdf)

"Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070544.pdf)

"SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070636.pdf)

"SUPAC-IR Questions and Answers about SUPAC-IR Guidance" (See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm)

"SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf)

"SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation" (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070930.pdf)

described in the current draft guidance are already included in the existing "Changes to an Approved NDA or ANDA" guidance. Yet, some of the annual reportable changes described in the "Changes to an Approved NDA or ANDA" guidance are not contained in the current draft guidance, such as a move to a different manufacturing site for secondary packaging or labeling. To avoid the confusion likely to stem from the availability of multiple guidances that cover the same topics, we recommend that these guidances be consolidated as appropriate and as soon as possible.

2. In addition to consolidation of advice on post-approval manufacturing changes into a single guidance document, FDA should consider evolving to the format adopted by Health Canada in its guidance entitled, "Post-Notice of Compliance Changes: Quality Document." This single guidance document, in addition to describing how Health Canada is to be notified of post-Notice of Compliance CMC Changes, also clearly demonstrates the relationship between regulatory relief and the need for additional data. (See http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.pdf)

3. At line 131 the guidance recommends that CMC annual reportable changes be supported by (among other things) a reference to affected validation protocols, standard operating procedures, and policies. These documents are frequently updated and revised. Currently, except for certain specific categories of products (i.e., natural products, recombinant DNA-derived proteins/polypeptides, complexes or conjugates of a drug substance with a monoclonal antibody), GMP/Compliance regulations require this information to be kept on file and presented to FDA upon request (for example, during an inspection). We are concerned that this general recommendation has the potential to increase industry's regulatory reporting burden. We recommend modifying the recommendation to include reference reflect the regulatory requirement as stated at 21 CFR 314.70(d)(3)(v).

Specific Comments – Appendix A

1. Regarding the Manufacturing Sites Section: Please also add deletion of a manufacturing or testing site as a change that can be annual reportable.

2. Regarding the Manufacturing Process Section: Please clarify whether item 3.2 ("A scale change of pooled or separated batches to perform the next step in the manufacturing process if all batches meet the approved in-process control limits and the critical operating parameters for the next step remain unaffected."), is intended to apply to any scale. (In Canada scale changes greater than 10% require prior approval.)

3. Regarding the Specifications Section:
   a. Item 4.1 describes the addition of a specification for existing excipients as annual reportable. Consider revising this statement to cover several types of changes to the specifications of existing excipients (e.g. addition, deletion, widening, or tightening of tests).
   b. Item 4.2 reads, "Change to a drug substance or drug product to comply with the official compendia can be reported in an annual report if it is:" Consider revising this statement

to read, "Change to a pharmacopeial excipient, drug substance, or drug product to comply with the official compendia can be reported in an annual report if it is:"

c. Consider revising item 4.5 to read, "Addition or replacement of an equivalent in-process test."
d. Consider including the deletion of alternate methods as an annual reportable change.
e. Please also consider making a change from an in-house method to a compendial method for excipients, API, and drug product as an annual reportable change.

4. Regarding the Container/Closure System section:
   a. Please clarify the meaning of the term "bottle dunnage," as it is used in the context of item 5.3.1.
   b. Consider modifying item 5.5 to also allow certain changes to the labeling on ferrules or caps. As an example, if a company were to remove the words "Flip Off" or a company logo from a product cap, the resulting impact to the drug product would have a minimal potential to have an adverse impact on its identity, purity, strength, quality, etc., thus one would expect this change to be annual reportable. This example is particularly relevant because USP appears to be moving forward on restricting the kinds of wording and logos that can appear on injectable product caps and overseals. We also recommend that a change to the color of the overseal be annual reportable.
5. Regarding the Miscellaneous Changes section: Item 6.1 says extension of expiry based on real-time stability data from pilot scale batches following an approved stability protocol is an annual reportable change. Please clarify how many batches are needed to support this annual reportable extension of expiry. (In Canada full long-term, real-time stability data for at least three commercial lots are needed, along with 24 months of shelf life, to support an annual reportable increase in shelf life.)

Thank you for the opportunity to comment on this matter. Should you have any questions, please contact Melodi McNeil at (301) 255-0080 or by FAX at (301) 255-0090.

Sincerely,

Mark Goldberger MD, MPH
Divisional Vice President
Regulatory Policy and Intelligence