



Date: MAR 06 2007

Food and Drug Administration
Division of Dockets Management, HFA-305
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: [Docket No. 2006N-0525]

Dear Sir or Madam:

Reference is made to the Federal Register Notice, Volume 72, No. 3 published on January 5, 2007, which solicits public comment about *Supplements and Other Changes to an Approved Application*.

AstraZeneca is grateful to the FDA for the opportunity to comment on the potential revision of 21CFR 314.70 and is highly supportive of the FDA's efforts to revise the regulation. An attachment of general and specific comments follows this cover letter.

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Please direct any questions or requests for additional information to me, or in my absence, to Norbert Ealer, Director, Regulatory CMC at 302-886-7633.

Sincerely,

A handwritten signature in black ink, appearing to read "Carol Stinson" followed by a flourish.

Carol Stinson, Sr. Director, Regulatory CMC
Regulatory Affairs
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Federal Register notice January 5, 2007 [Docket No. 2006N-0525]
Supplements and Other Changes to an Approved Application

AstraZeneca is grateful to the FDA for the opportunity to comment on the potential revision of 21CFR 314.70 and is highly supportive of the FDA's efforts to revise the regulation.

General Comments

AstraZeneca does not consider these proposals to represent "de-regulation", but instead the proposed approach is considered to represent smarter regulation, in full alignment with the "GMPS for the 21st Century" and the FDA's "Critical Path Initiative."

A reduction in the number of manufacturing supplements prepared by industry and reviewed by FDA should be the highest priority. Many supplements created now are "non value-added", not related to real patient risk and attention to these drains resources from both industry and FDA.

It is essential that advances in manufacturing sciences, quality risk management and pharmaceutical quality systems be complimented by a regulatory environment that encourages Industry to introduce continual improvement and innovative technologies to the manufacture and control of their processes. We believe that the successful implementation of the concepts outlined in ICH Q8 and Q9, as well as those anticipated in Q10 Quality Systems, will enable the desired regulatory environment to become a reality. With these in place, we believe a firm should be more empowered to self-manage changes, as articulated in the FDA's 'Desired State'.

Following the proposed revisions to 314.70, product quality will continue to be assured by the manufacturer. All of the proposed revisions to the regulation drive toward a positive change, with benefits for industry, regulators and ultimately the patient, with the following underlying principles being key:

- Ensure the continued protection of public health
- Simplify and clarify regulatory procedures for post-approval changes
- Encourage and enable innovation and continual improvement in pharmaceutical development and manufacturing
- Reduce the number of regulatory events associated with post-approval changes and the associated regulatory burden
- Facilitate rapid implementation of beneficial changes that have no potential to impact on patient safety or that reduce any potential risk
- Enable clarity and predictability of regulatory requirements
- Support global harmonization of the approach to post-approval changes
- Apply the same fundamental principles to changes to biological products, as those used for changes to medicinal products containing conventional (small molecules)

Specific Comments

- Revision of the regulation must provide flexibility to take into consideration changes to: “traditional” submissions (e.g. not containing elements of Quality by Design (QbD)), QbD submissions, as well as hybrids between these two extremes. In short, the system should reward science and risk-based application of product knowledge, use of Quality Risk Management and use of a Pharmaceutical Quality System with a different degree of regulatory oversight and provide a mechanism for greater self-management of changes by industry. Regulatory oversight could be focused on inspections of the firms PQS, rather than submission and review of changes.
- The new regulation should help facilitate QbD approaches and demonstrate the benefits of investing in manufacturing science and pharmaceutical quality systems.
- Post-approval changes should be based on product specific ‘regulatory agreements’. This would be developed as a specific component of the NDA submission, or as a supplement for an existing product, and form the basis for reducing post-approval change reporting and review requirements.
- The use of ‘generic’ comparability protocols, setting out in advance the acceptance criteria for a change(s) should be explored in tandem with the ‘regulatory agreement’. This would allow a firm to affect a change(s) in a timelier manner.
- It is recommended that the new regulation reduce or remove “reporting categories” that are not necessary and the reduction or elimination of Changes Being Effected (CBE) Supplements (0 and 30) is supported.
 - We propose a ‘do and tell’ (notification) approach for changes assessed by the firm as having a lower risk of impact on the key product quality attributes. Do and tell is either immediate notification to the FDA (a category similar the CBE-0, except that the current CBE-0 ultimately requires “approval”, whereas the proposed immediate notification category does not) or the firm notifies the FDA periodically (e.g. the Annual Report).
 - A prior-approval route should be limited to changes with a higher risk of impact upon the key product quality attributes that are not covered by the regulatory agreement/comparability protocol.
 - The proposal to eliminate the intermediate filing category of CBE-30/CBE-0, as it is today, should not automatically result in the default for “medium risk changes” to require prior-approval supplements.

- Proposed changes that ensure greater product quality should not require supplements. For example, in 21 CFR314.70:
 - (c)(1), which refers to Special Supplement—Changes Being Effected; “Adds a new specification or test method...to provide increased assurance that the drug will have the characteristics... it purports...to possess.”
 - (d)(1), which refers to changes in an Annual Report; “any change made to comply with an official compendium.”

In these two examples, time and resource for both industry and FDA are being wasted reporting and reviewing changes that only assure greater quality. These should be eliminated.

- Revision of statements not consistent with a risk-based approach is recommended. Language that is vague, e.g. “that may affect” (21 CFR314.70 b.2.iv) or language that describes change as “substantial potential to affect” should be removed and replaced with risk management language. In addition, it is recommended that specific change examples be removed from the regulation and appear instead in guidances, when necessary, to illustrate the FDA’s view.
- The format and content of NDA Annual Reports should be revised. The process could be streamlined by including only an “Index of Changes” to the Center, while supporting data would be available upon FDA inspection. Consideration should be given to integration of the NDA Annual Report and the Annual Product Review, with a preference to eliminate one of these and revise the other. Consideration should be given to global coordination of timing of the annual report/product review and emphasis should be placed upon inspection of the quality system, rather than filing and review of lists.
- A different approach to classifying manufacturing sites is suggested, based upon a sponsor’s global and local quality system rather than the dosage form(s), which are made at that site(s). Manufacturer’s who demonstrate knowledge management and change management through a quality systems approach and application of risk management should receive less regulatory oversight as an incentive for embracing a science-based and risk-based approach. This approach could be coordinated with certification of ICH Q10 principles at the site and should further enable site-to-site transfers with reduced regulatory oversight.
- Consideration should be given to application of research outcomes and opportunities sought to further reduce filing requirements when scientific research provides conclusions that an actual risk associated with specific pharmaceutical changes is less than previously perceived (e.g. packaging changes).

- Continual emphasis should be placed on changing the language in Guidance Documents from prescriptive to conceptual. Case study examples, which demonstrate post-approval changes that are “notification only” or those requiring FDA interaction, should be included in new guidances.
- Revision to the DMF review system should be coordinated to maximize risk-based approaches and to save FDA and industry time, such that when a DMF reference is included in an NDA or sNDA, lag times for DMF holder responses to deficiencies are reduced or eliminated.
- It is essential that FDA continue to harmonize their efforts to reform the US post-approval system with the ongoing efforts globally to do the same (e.g. EU Variations proposals). In this regard, the EFPIA position on Variations should be considered, and are as follows:
 - Promotes a risk and science-based approach
 - Builds upon the concepts of ICH Q8, Q9, and Q10
 - Should encourage and enable innovation and continuous improvement
 - Based on 2 variation categories:
 - Minor changes according to ‘do and tell’ or notification (immediate or periodic); Industry default is a notification
 - Major changes requiring prior-approval
 - Introduces the concept of a Regulatory Agreement and links specific changes to appropriate risk assessment of the change
 - Facilitates a single assessment for a change which affects many products e.g. key intermediates, container and closure
 - Facilitates improvements in the DMF system to synchronize review of DMFs to marketing application reviews.
 - Extends the EU DMF system to capture supplier information, e.g. container and closure components.