

Division of Dockets Management (HFA-305)
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852



March 7, 2007

Re: Docket No. 2006N-0525

SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION

Dear Sir/Madam:

Schering-Plough has reviewed the Federal Register Notice of January 5, 2007 concerning potential revisions to the post-approval Chemistry, Manufacturing and Controls (CMC) regulations. The following comments are being provided for FDA's consideration to the above referenced docket.

Schering-Plough supports CDER's initiatives to revise the existing regulations regarding post-approval CMC supplements and other changes to approved applications. We believe there are many opportunities to reduce the current post-approval reporting requirements without adversely impacting product quality or patient safety. A reduction in post-approval reporting should not only apply to new products developed under the principles of Quality by Design (QbD), but also to traditionally developed products applying existing knowledge and risk-based quality management principles.

Schering-Plough acknowledges that manufacturers are ultimately accountable for providing safe and effective drugs of the highest quality and we take this responsibility seriously. We have instituted a comprehensive quality systems (QS) approach in the manufacture of human and veterinary drug products based on the Agency's guidance to meet the requirements of current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211). Our change management system forms a key component of the QS model and is used to evaluate post-approval changes. We categorize changes into different levels based on their impact to product quality. Principles of risk management and quality systems are applied in review of changes by a cross-functional technical team. Supportive data and technical justification are required to support a proposed post-approval change regardless of the regulatory reporting requirement. S-P is committed to continuing this activity regardless of post-approval change reporting requirements. Once a change is authorized internally, appropriate data and supporting documentation are submitted to the Agency, as required.

Schering-Plough believes that all post-approval changes could be grouped into two reporting categories, instead of the three that exist within the current regulatory framework. With a robust Quality Management System in place, a risk-based approach can be used to determine the appropriate reporting category by leveraging existing developmental data, technical/scientific evaluations, prior knowledge with similar products, as well as supporting data from a product's commercial manufacturing history. After a thorough internal review of the change justification, scientific rationale, and impact assessment, a firm can classify certain changes as Prior Approval Supplements or Annual Reportable based on the impact to product quality and/or patient safety. This

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approach can be used today for traditionally-developed marketed products and will help establish the foundation for new products developed according to the principles of Quality by Design.

Schering-Plough conducted a historical review of recent changes that were filed as either Prior Approval or Changes Being Effectuated Supplements. The following examples are included to illustrate the types of changes that we believe pose a low risk in terms of impact to product quality and/or patient safety. We would recommend that these types of changes be filed in the Annual Report:

- Release specification changes that improve quality control; for example, the addition of a test to improve quality control of a product.
- Removal of a manufacturing, packaging, or testing site from an application, when an alternative qualified site is included in the application.
- Changes in equipment design for a non-critical step in the process.
- Changes in the order of addition of ingredients for solution dosage forms.
- Removal of the intermediate stability interval for a product with a well-established stability history.
- Introduction of a new product or line extension into a multi-use facility, which has been producing similar products.
- Changing an analytical testing facility to one with a positive FDA inspection history.

Schering-Plough also conducted a similar review for Biological Pharmaceutical products. We believe that the above mentioned changes should also be considered for reduced reporting requirements for biologics. Historically, changes normally covered under GMP's have required supplemental applications for biological products. These types of changes also present a low risk and should be considered for reduced reporting requirements. Examples would include:

- Introduction of new products into an approved manufacturing area
- Updates to environmental monitoring programs
- Minor facility and equipment modifications

Using the risk-based approach for evaluation of changes for Biological Pharmaceuticals would harmonize the approaches for small molecules and biologics.

Regarding Compendial changes, Schering-Plough recommends that the regulations be revised to allow for no reporting requirement for certain compendial changes. Reporting of compendial changes in an NDA or ANDA should be relevant to the information in the filing. If the regulatory filing contains no detail other than citing the USP or NF monograph or a USP or NF General Chapter, then there is essentially no change to the regulatory filing. The expectation is that the firm is in compliance with the current compendia. This compliance may be confirmed during routine GMP inspections.

Schering-Plough supports the opportunity to potentially harmonize CMC post-approval changes with other regions due to the timing of 21 CFR 314.70 revisions with initiatives in other countries (e.g., Europe). As a pharmaceutical company that supplies products to the global marketplace, the current post-approval change situation involves navigating differing regulatory requirements in various regions for the same change. This presents an onerous challenge for moving forward with innovation and updates to existing

products and processes. Harmonizing requirements would lessen the time and resources consumed with generating and assembling different technical data packages, thus providing the opportunity to focus on process and product improvements.

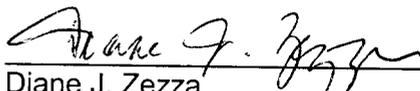
As a long term goal, we feel that harmonization of post-approval change requirements across regions is vitally important.

Based on the above discussion, Schering Plough agrees that a re-write to the existing 21 CFR 314.70 regulation is appropriate. We also concur that the current text in 21 CFR 314.70 is prescriptive and categorizes post-approval CMC changes and their reporting requirements without consideration of the applicant's risk management activities or internal quality systems.

Schering-Plough would envision a re-written 21 CFR 314.70 to be more general in context and eliminate the specific categories currently listed. The revised regulation should incorporate a risk-based approach that considers product and process knowledge as well as scientific evaluations to determine the regulatory filing category. The technical evaluation, which demonstrates that a change has had no adverse impact on product quality, would serve as the basis for a reduced filing category.

It is thought that 21 CFR 314.70 could be drafted in the spirit of the regulations laid out in 21 CFR 210 & 211 (cGMPs). The GMP regulations identify a number of general requirements however, does not dictate how sponsors ensure compliance.

It should also be noted that the prescriptive nature of 21 CFR 314.70 is apparent in the Guidance for Industry - Changes to an Approved NDA or ANDA (April 2004). Schering-Plough would expect a revised/new guidance be drafted that is aligned and consistent with the new 21 CFR 314.70.



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