

Pfizer Comments to Supplements and Other Changes to an Approved Application

Docket No. 2006N-0525

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Pfizer supports FDA efforts to implement science- and risk-based approaches to improve and streamline the regulatory process for post-approval manufacturing and control changes to an approved application. We strongly endorse the PhRMA perspective on this subject that was presented at the FDA Public Meeting on February 7, 2007. Pfizer suggests that modifications to the existing process for post-approval changes to an approved application could be expeditiously addressed by issuance of a new guidance document, and that the regulation in 21 CFR 314.70 be revised at a later date if necessary for consistency.

For industry or FDA to gain any significant benefit with regard to reducing the number of manufacturing supplements, this new approach must be applicable to existing products with "conventional" applications. With robust internal quality systems in place, a manufacturer should be allowed to implement post-approval changes that do not impact safety or efficacy without submission of a supplement.

Therefore, Pfizer proposes a two-tiered approach to post-approval changes: prior approval and the annual report. Collaboration between the agency and industry should result in a limited number of significant changes or critical situations that would require prior approval by FDA; all other changes should be managed by the firm's quality system and reported in the annual report. We further suggest that the format of the annual report be revised to require only a list of the changes implemented, and that data and supporting documentation be retained at the site for agency monitoring during the periodic inspectional review.

For newer Quality by Design (QbD) applications that contain substantially increased product knowledge, the expectations for post-approval supplements should be based on the availability of enhanced process and product understanding that is included in the registration dossier. For QbD based submissions, the process for how the sponsor will manage post-approval changes should be described in a "regulatory agreement" between the Agency and the sponsor.

Pfizer recognizes that the maximum benefit for industry would be in a post-approval change system which is globally aligned. However, we also recognize the importance of progress in the near term, and therefore, we support proceeding with appropriate revision to the current US post-approval process at this time, while continuing the agency's efforts, both within and outside of the ICH process, to gain global alignment.

Questions to be answered:

1. Is it valuable for the agency to move toward a more risk-based and quality systems oriented strategy for regulating post approval CMC changes outside of the formal application review process? What are the advantages and/or disadvantages?

As indicated in the general comments above, it is valuable for the agency and industry to provide further enhancements to the current approach to post-approval change management. An applicant should be able to gain agency confidence for change management approaches, which are founded upon and utilize combinations of product specific knowledge, risk management, enhanced controls and enhanced quality system, to require less regulatory oversight. In addition, as new products are submitted, for which there is enhanced product and process understanding, the strategy for regulating post-approval CMC changes can become more risk-based and quality systems oriented. In both cases, the advantage is fewer supplements to be prepared and reviewed by industry and the agency respectively. Also, reducing the need of post-approval supplements would facilitate continual improvement and technical innovation.

Pfizer respectfully suggests that for the initiative to update § 314.70 to be successful, public workshops need to be organized for industry and regulators to work together.

2. Would revising § 314.70 as described in this notice provide the same level of protection to the public as the current regulatory scheme with respect to ensuring the safety and efficacy of human drugs? What inspectional approaches might the agency consider to evaluate manufacturing changes while ensuring public safety?

Revision to § 314.70 as suggested in the general comments would result in an increase to public safety. Thorough FDA review of those changes that could impact the safety and efficacy of the product would maintain focus on those changes that are of greater importance, and reduce dilution of the overall efforts of the agency. Moreover, the reduction in overall efforts by the agency relative to review of changes would allow FDA to reallocate resources to act on more significant matters of public concern. Implementation of the proposal in the general comments can be evaluated by FDA's investigators during routine inspections to ensure compliance with current standards and the firm's internal quality system.

3. Would revising § 314.70 as described in this notice change the regulatory burden on the pharmaceutical industry? If so, how would the burden change?

Revising § 314.70 as indicated in the general comments should facilitate a reduction in the regulatory burden. However, to gain significant benefit, changes to § 314.70 should clearly include a mechanism for updating applications for legacy products as well as those designated as "QbD." To further reduce the regulatory burden for industry, there should be global harmonization on post-approval supplements.

4. Would reducing the prescriptiveness of § 314.70 provide manufacturers with greater regulatory flexibility? Would it encourage manufacturers to adopt CMC-related risk management strategies? Would there be disadvantages?

Reducing the prescriptiveness of § 314.70 would provide greater regulatory flexibility. Pfizer supports the writing of high level regulations which would be supported by detailed guidances. As sponsors assume greater responsibilities for post-approval change management, they would be encouraged to strengthen their internal quality systems and apply science-based and risk-based approaches to manufacturing, which would facilitate continual improvement and technical innovation.