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March 6, 2007

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2006N-0525, January 5, 2007 (72 FR, 574-576)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments in response to the Agency's request for input on questions presented in Section II (Questions for Discussion and Comment) of the January 5, 2007 Federal Register notice entitled, "Supplements and Other Changes to an Approved Application."

Wyeth is one of the largest research based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications. Wyeth appreciates the opportunity to comment on the above-mentioned topic; our comments are provided below.

GENERAL COMMENTS

Wyeth fully endorses the Agency moving towards a more risk-based and quality systems oriented strategy for regulating postapproval CMC changes. We believe that revision of § 314.70 would definitively establish the foundation for quality by design (QbD), reinforce the objectives of ICH Q8, Q9, and Q10, and would encourage Industry to gain an increased understanding of drug product development and manufacturing processes to move towards a QbD approach.

We urge the FDA to not limit the revision to 314.70 but also apply it to 601.12 and associated regulations for combination products to ensure regulatory consistency in handling manufacturing changes and alignment with international harmonization initiatives (i.e., ICH Q8, Q9, and Q10). All comments provided herein are intended to apply to 314.70 as well as 601.12 and combination products.

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**SPECIFIC COMMENTS**

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

We support the Agency adopting a more risk-based approach and quality systems oriented strategy for regulating postapproval CMC changes. This approach can reduce the number of supplements submitted and lead to earlier implementation of improved manufacturing processes, which can translate into greater public health benefits (e.g., high quality drug product is made available to the public without delay). In addition, we believe that FDA will also be able to focus its scientific review resources on the review of more complicated manufacturing changes that represent a higher risk and would still require a prior approval supplement.

Initially, companies and FDA may require additional resources to better understand and implement a risk-based approach to product development and manufacturing, however, it is expected that as this approach becomes more widely accepted, the resources and time required would decrease. However, while the number of supplements submitted may decrease, the review of the annual reports by the Agency may become more robust and therefore require a shift in FDA resources.

To minimize the degree of risk, we recommend that the Agency issue guidance that includes specific examples defining appropriate areas for regulatory flexibility (e.g., identification of critical sources of process variation) and how to evaluate risk and document a risk assessment when using this type of approach (e.g., using the risk assessment tool to demonstrate risk mitigation). The recommendations should be generated with input from Industry and FDA.

- 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?

We believe revising 314.70, as well as 601.12 and coordination with combination products, is consistent with the objective of the Agency's "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" and supports the incremental adjustments in FDA's regulatory approach to product quality while ensuring the safety and efficacy of human drugs. Risk assessments combined with risk mitigation, pharmaceutical development and quality systems as documented in ICH Q8, Q9, and Q10 constitute a more thorough and interwoven approach than just

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using the current CBE/CBE-30 and PAS approval mechanisms to support post approval changes. We acknowledge that implementation of these approaches may depend upon a company's knowledge and experience; however, risk can be minimized by the development of guidance as recommended above and holding public workshops to increase Industry and FDA knowledge on the implementation of revised regulations.

Inspectional approaches should focus on change control, the company's approach to risk management, and annual product reports. We recommend that inspections be risk-based and considerations should be given to redirecting resources away from low risk areas and towards higher risk areas (e.g., sterile products, novel therapies).

- 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?

As noted in response #1 above, we believe that revising 314.70 and 601.12 and coordination with combination products will reduce the regulatory reporting burden by reducing the number of supplements and ultimately lead to earlier implementation of improved manufacturing processes. However, revising 314.70 would increase the requirement to document changes and demonstrate a thorough risk assessment and risk mitigation plan to ensure that an acceptable level of risk can be appropriately managed. Furthermore, we believe that revising 314.70 may initially increase the resources needed to perform initial quality and risk assessments, ensure manufacturing processes are fully understood, process controls are implemented in a compliant fashion, and design spaces are developed for unit operations. However, with increased understanding of the manufacturing process, this regulatory burden would reduce over time.

To clarify the regulatory reporting requirements, we recommend that the Agency revise 314.70 to reflect CBE and CBE-30 supplements as annual reportable to reflect a more risk-based and quality systems oriented strategy for regulating postapproval CMC changes.

- 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 manufacturers with greater regulatory flexibility and encourage companies to adopt risk-management strategies for process improvements. However, the impact may not be fully realized by smaller companies with fewer resources to adopt and implement these strategies. At this time, it is not clear what amount

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of process and product knowledge is needed to attain regulatory flexibility. To better clarify the relationship between the degree of process understanding and regulatory flexibility, we recommend that the Agency, in consultation with Industry, develop a SUPAC-like guidance on this topic.

We are submitting the above comments in duplicate. Wyeth appreciates the opportunity to comment on the above mentioned draft guidance and trusts that the Agency will take these comments into consideration.

Sincerely,



Roy J. Baranello, Jr.
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