



Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.1000

Date: March 6, 2007

Subject: Docket No. 2006N-0525
Potential Revision to 21CFR 314.70, FDA request for comment published in Federal Register

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA, which strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to dramatically improve people's lives.

We are pleased to provide the attached comments on the questions which FDA has posed regarding a possible rule change to 21CFR 314.70.

We support FDA's intended approach to revise reporting of post approval changes to reflect a risk based approach supported by product and process understanding.

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Karen Parker at (805) 447-2765.

Sincerely,

A handwritten signature in cursive script, appearing to read "Karen Parker".

Karen Parker
Amgen Global Regulatory Affairs

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?

Amgen fully supports the agency's proposed move toward a more risk-based quality systems approach for regulation of post-approval CMC changes. We support implementing this approach on a product by product basis upon either initial product application or through a prior approval supplement. The extent of flexibility should be based on the in depth product and process knowledge that is obtained by following the principles and practices of Quality by Design, in addition to consideration of the GMP compliance status of the manufacturer.

We suggest that the option for regulatory flexibility be an *alternative* to the existing process because it is not likely to be applicable to all manufacturers of all products in the near future. The agency should anticipate a phased implementation of this risk based approach and in depth product and process knowledge within the industry. For those products where more limited process and product information is available upon approval or where an adequate compliance history has not yet been established, application of the existing standards to review and approval of changes may be appropriate. If both options are retained this will ensure commercialization of important life-saving medications.

Amgen encourages FDA to identify a mechanism, or provide a legal avenue, to apply this approach to both recombinant DNA derived therapeutic products and monoclonal antibody derived products approved in a BLA but currently regulated by CDER. Further, we suggest that FDA remove all CBE changes from reporting requirements, independent of product or manufacturer. These changes could either become annual reportable or could be subject to evaluation during GMP inspections.

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?

Amgen strongly agrees that revisions may be made to the process of implementing post approval changes while ensuring FDA's responsibility or ability to protect the public. FDA must ensure that new medicines to treat disease are demonstrated to be safe and effective and are approved in a timely manner. FDA oversight of post approval changes should be consistent with the risk to public health and can be managed by applying flexibility on a case by case basis. Further, this earned flexibility encourages industry to adopt new technologies and process improvements.

One of the challenges to implementing this type of change will be to ensure consistency in approach among the GMP inspectorate. Inspectors have different understanding of what constitutes adequate risk management and optimal quality systems. This potential inconsistency will be minimized if FDA documents the specific regulatory flexibility in

an approval letter, either the original letter or as approval to a prior approval supplement. In this way, both industry and the inspectorate will have a clear, documented understanding of the reporting requirements established by the product reviewers for that product and manufacturer. Further, this approach to implementation of CMC based post approval changes ensures linkage to the initial safety and efficacy review of the product.

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?*

Uncertainty in inventory and production planning are often barriers to implementing change. The proposed revision to 21 CFR 314.70 to minimize the need for prior approval supplements will moderate this uncertainty and will be a significant advantage to industry.

The industry will, however, continue to document changes, their justification, and generate the necessary data to demonstrate that there is no impact to product quality. If as suggested, FDA converts all CBE changes from reporting requirements to annual reportable or data that would be subject to evaluation during GMP inspections, the burden on the regulated industry would be minimally reduced as a result of the proposed changes. The major impact would be a reduction in uncertainty with respect to inventory management.

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?*

Manufacturers will have additional motivation to adopt a CMC-related risk management approach if regulatory flexibility is the incentive for adopting the approach. To achieve the full benefits of flexibility, manufacturers will need to invest resources earlier in the development process to ensure a sound scientific understanding of products and processes. Many post approval manufacturing changes such as changes made to increase yield, shorten cycle time, and optimize use of limited resources including facilities and equipment are business driven while assuring product quality. The decision for a company to implement a sound risk management program and in depth process understanding will be a balanced decision driven on the extent of flexibility granted by the regulators.