AMGEN

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.2617
mfeild@amgen.com
www.amgen.com

4 November 2003

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Reference: **Docket No. 2003D-0380**
Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Amgen would like to provide comments on the recently issued draft Guidance for Industry entitled "PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance." A team of experts in this field prepared the comments that follow.

Amgen is encouraged by the willingness of the agency to assist in promoting the use and adoption of this technology in our industry. As the world's largest biopharmaceutical manufacturer, Amgen supports the development and implementation of PAT for use in the manufacture of biotechnology and pharmaceutical products and offers these comments for your consideration. Amgen would be willing to work with the agency to develop guidelines for PAT application in the more complex products that biotechnology tends to produce.

Specific Comments:

1. Multivariate Data Analysis and Tools: Lines 300-315 describe that a knowledge base can be of benefit during regulatory decision-making. Some additional guidance concerning the elements of the knowledge base might be used should be included in this section. Also, knowledge-management systems are mentioned as being an important element. Some examples of these would also be helpful. The description of design of experiments identifies the possible interactions between product and process variables. The term used to describe this in statistics is 'confounding effects'. To avoid confusion, Line 322-324 may be written as: "These interactions, or confounding effects, essentially are the inability...."
2. "Risk analysis" (line 384) or "risk-based regulatory approaches" (Line 145) is used multiple times in the guidance. References or specific descriptions of what risk-based regulatory approaches are and how they might apply in PAT would be very helpful.
3. The following terms are used within the guidance and are probably going to be some of the more difficult concepts to define and for establishing specifications. It will be especially true for existing products where specifications already exist based on current conventional technologies. These terms are partially or not defined. To avoid confusion, they should be defined perhaps as part of a glossary.

- Real time release
- Continuous real time quality assurance

4. Concerning specifications for release, how might the application of PAT change the way specifications are written? This needs to be addressed for the 'conversion' of existing approved products to using PAT applications as well as for new products/processes that are to be filed. Lines 682-685 speaks only to currently approved products and that manufacturers should 'consider' how PAT might affect specifications as well as in-process controls. Some guidance on what regulatory specifications might look like would be helpful.

5. The validation of PAT applications in a process is complicated by the fact that introducing sensors or probes into process equipment for on-line or in-line testing, may impact already validated processes. Also, having to validate the location and orientation of the sensor/probe is complicated by an inability to easily and/or extensively modify equipment at production scale to qualify their locations and placements. These issues have been highlighted at several joint industry/FDA-sponsored conferences. The guidance could benefit from some more details concerning how to approach these issues and what types of discussions a sponsor should have with the agency in developing a PAT application within their process.

6. The guidance vaguely addresses being able to work under a "research exemption" during development of PAT applications. This has been communicated vebally at workshops on PAT but is not specifically detailed here. (Lines 626-647). Discussions held on applying PAT has hinted that many sponsors may be unwilling to investigate the potential of these technologies and therefore slow experimentation with and implementation of them due to the uncertainty around the impact on existing approved products. More direct discussion is desirable on the impact of PAT and how it may or may not affect an approved product's compliance with regulatory specifications.

7. More detail and specific examples of the different types of multivariate data acquisition and analysis that may be applied to PAT would be helpful. The types of analyses mentioned at workshops as being powerful and more useful for PAT such as chemometrics, partial least squares analysis, and principle component analysis are absent from the guidance. They should be mentioned and described in some detail as to how PAT may utilize them.

8. For the regulatory filing process, it would be helpful to outline how the process would work. In lines 650-685, the guidance mentions that close communication is a key component of the regulatory approach. This indicates that the approach is still vague and not well defined. Since any PAT application will impact existing and new products, some description or examples of how each type of filing might be handled would be helpful.

Amgen Inc. appreciates the opportunity to support the FDA in the preparation of sound and science-based guidance. If you require further information, please feel free to contact me at (805) 447-2617or mfeild@amgen.com.

Sincerely,

for Mark Feild

Mark J Feild, PhD
Associate Director
Corporate Validation Systems

(2003-1104 Amgen Comments on PAT draft guidance)