



22 10 '04 11 30 11 31

November 29, 2004

Via fax and UPS

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

Re: Docket No. 2004D-0443

Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations [Federal Register Volume 69, No. 191, pages 59256, October 4, 2004]

Dear Sir/Madam:

Aventis Pharmaceuticals appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "*Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*".

This draft guidance describes the key elements of a robust quality systems model and shows how persons implementing such a model can achieve compliance with the CGMP regulations.

In general, the guidance draft provides a good summary and is to be applauded.

SPECIFIC COMMENTS:

II. BACKGROUND AND PURPOSE

B. Goal of the Guidance

Lines 98-103: *The FDA has concluded that modern quality systems, when coupled with manufacturing process and product knowledge, can handle many types of changes to facilities, equipment, and processes without the need for a regulatory submission. Manufacturers with appropriate process knowledge and a robust quality system should be able to implement many types of improvements without the need for a prior regulatory filing. In addition, an effective quality system, by lowering the risk of manufacturing problems, may result in shorter and fewer FDA inspections.*

Aventis request further clarification regarding the statement on the ability to implement changes without prior approval. We suggest defining some examples for changes without prior approval, e.g. in an appendix.

2004D-0443

C 3

Lines 118-119: *This document is **not** intended to create new expectations for pharmaceutical manufacturing that go beyond the requirements laid out in the current regulations nor is the guidance intended to be a guide for the conduct of FDA inspections.*

This text gives rise to the expectation that employing a quality system according to this guideline will lead to relief regarding inspections and regulatory burden. This is very positive. However, we request further clarification of this statement and suggest that FDA provides tangible examples.

C. Scope of the Guidance

Lines 115-116: *It may also be useful to manufacturers of components used in the manufacture of these products.*

We request clarification on whether this applies to API manufacturers. As the sentence is written, the language indicates that there is no difference seen between the API, excipients, process support materials (e.g. Nitrogen), and primary or secondary packaging.

III. CGMPs AND THE CONCEPTS OF MODERN QUALITY SYSTEMS

F. The Quality Unit

Lines 234-235: *Under a robust quality system, the manufacturing units and the quality unit can remain independent, but still be included in the total concept of producing quality products.*

We request further clarification on what is meant by “*manufacturing units and the quality unit can remain independent*”? What would be the preferred alternative?

IV. THE QUALITY SYSTEMS MODEL

C. Manufacturing Operations 1. Design and Develop Product and Processes

Lines 543-547: *In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined, from design to delivery, and control should be exercised over all changes. Quality and manufacturing processes and procedures — and changes to them — should be defined, approved, and controlled (CGMP also requires this; see § 211.100).*

We suggest including development, not only design, for addressing pharmaceutical manufacturing.

C. Manufacturing Operations 4. Perform and Monitor Operations

Lines 652-654: *In a quality system, process validation provides initial proof, through commercial batch manufacture, that the design of the process produces the intended product quality.*

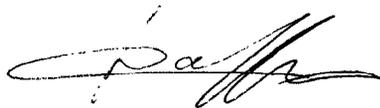
This text indicates that prospective process validation is always necessary prior to marketing. This conflicts with the new validation policy guide and therefore, Aventis recommends adapting the text to the validation policy guide. We also requests clarification that new technology and manufacturing science application can eliminate the need for conformance batches prior to marketing.

Lines 677: *Process steps should be verified using a validated computer system or a second person.*

We suggest adding “critical” as the first word of the sentence since only “critical process steps” should be monitored with a second signature.

On behalf of Aventis Pharmaceuticals, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* and are much obliged for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Caffé', with a stylized flourish extending to the right.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs