Aventis Pharmaceuticals

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April 25, 2003

Via fax and UPS

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

Re: Docket Nos. 03D-0060, 99D-1458, 00D-1538, 00D-1543, 00D-1542, and 00D-1539
Draft Guidance for Industry on Part 11, Electronic Records, Electronic Signatures – Scope and Application [Federal Register Volume 68, No. 37, page 8775, February 25, 2003].

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Part 11, Electronic Records, Electronic Signatures – Scope and Application".

This draft guidance provides recommendations on FDA's current thinking regarding the requirements and application of Part 11 (21 CFR Part 11). This draft guidance announces that the Agency intends to exercise enforcement discretion with respect to the validation, audit trail, record retention, and record copying requirements of Part 11.

We offer the following comments/clarification for your consideration.

General Issues

For more clarity, please provide additional examples in relation to the following topics:

- Required record is printed but nonetheless the firm rely on electronic record to perform regulated activities (lines 171-178)
- When a non-electronic audit trail is acceptable (lines 227-228)
- Additional examples to that provided in line 209-210 concerning validation
- Acceptable and unacceptable hybrid situation relative to record retention (lines 279-281)

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Section I. INTRODUCTION
Page 1, Line 21, Footnote 3

These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR part 21), the Quality System Regulation (21 CFR part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR part 58).

Is there a reason why these 3 regulations are cited as examples? Does this in any way imply FDA's focus (risk based approach) on certain regulations more than others?

Section I. INTRODUCTION
Page 1, Line 32, Footnote 4

See Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach at www.fda.gov/oc/guidance/gmp.html.

What does FDA mean by "Risk-Based Approach" in the context of P11? The attached reference talks about "Risk-base orientation", "Risk-based programs", "Risk-based control point analysis", "Risk management approach". A clear definition/guidance reflecting FDA expectation on Risk-Based Approach as it applies to P11 will be very useful.

As part of the Risk-Based Approach the Agency is planning to facilitate external review of the existing cGMP program, does the external review activity include the P11 program and what organizations will constitute the external review panel / committee

Is the Risk-Based concept limited to drug cGMPs or does it also apply to drug GCP and GLPs?

Section I. INTRODUCTION
Page 2, Lines 33-35

We may revise provisions of Part 11 as a result of that re-examination. This guidance explains that, while this re-examination of Part 11 is under way, we will narrowly interpret the scope of Part 11.

When will the final Guidance on P11 Scope and application be finalized?

When will we know if the P11 ruling will be revised?

When will the revised P11 ruling become effective if a determination is made to revise it?

Section I. INTRODUCTION
Page 2, Lines 36-38 and 41-44

We will not normally take regulatory action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of Part 11 as explained in this guidance.

In addition, we intend to exercise enforcement discretion and will not normally take regulatory action to enforce Part 11 with regard to systems that were operational before August 20, 1997, the effective date of Part 11 (commonly known as existing or legacy systems) while we are re-examining Part 11.

What does the Agency mean by the word "normally", what are the exceptions?

Section II. BACKGROUND
Page 3, Lines 82-86

Concerns have been raised that some interpretations of the Part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit.

How does the agency ensure that the envisaged Risk-Based Approach would not (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit?

Section II. BACKGROUND
Page 3, Lines 98-100

Accordingly, FDA is withdrawing those draft guidances and CPG 7153.17 as well as the guidance on electronic copies of electronic records.

In the absence of these guidances what will the field investigators use during Plant, Sponsor, and Clinical-Investigator-Site inspections? What will be the fate of other clinical or preclinical guidance documents that cover P11 issues and are currently in effect?

Section III. DISCUSSION
Part A. Overall Approach to Part 11 Requirements
Page 4, Line 124

FDA will enforce predicate rule requirements for records that are subject to Part 11.

Records are created to satisfy predicate regulations and hence they are subject to those regulations however this statement reads as though P11 is a predicate regulation which is in conflict with the statement in lines 28-29.

Section III. DISCUSSION
Part C. Approach to Specific Part 11 Requirements,
No. 1 Validation
Pages 5-6, Lines 198-205

The Agency intends to exercise enforcement discretion regarding the specific Part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)).

Even if there is no predicate rule requirement to validate a system in a particular instance, it may nonetheless be important to validate the system to ensure the accuracy and reliability of the Part 11 records contained in the system.

Which specific Part 11 requirements for validation of computerized systems (§11.10(a) and corresponding requirements in § 11.30) the Agency intends to exercise enforcement discretion?

Which are the applicable drug predicate rule requirements for validation that persons must still comply with?

If the underlying predicate rule does not require validation, and since Agency's suggestions on validation do not establish legal enforceable responsibilities, and the Agency will exercise enforcement discretion regarding the specific P11 requirements for validation, then what will be the compelling reason for persons to validate systems that fall in this category?

Section III. DISCUSSION
Part C. Approach to Specific Part 11 Requirements,
No. 2 Audit Trail
Page 6, Lines 231-232

Audit trails are particularly important where the users are expected to create, modify, or delete regulated records during normal operation.

What is Agency's expectation on application of audit trail, or other appropriate measures, to regulated Raw-Data records versus regulated Document records?

Section III. DISCUSSION
Part C. Approach to Specific Part 11 Requirements,
No. 5 Record Retention
Page 7, Lines 271-273

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

What is Agency's current thinking on "value of the records over time" from the regulatory compliance view point?

What is Agency's expectations regarding documented risk assessment to justify the decision on how to maintain records?

How will the Agency apply enforcement discretion on this topic?

Section III. DISCUSSION
Part C. Approach to Specific Part 11 Requirements,
No. 5 Record Retention
Page 7, Lines 275-277

FDA normally does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format, such as PDF.

What does the Agency mean by the word "normally", what are the exceptions?

REFERENCES
Other U.S. Federal References
Page 9, Lines 305-307

5. *NIST Special Publication SP800-30: Risk Management Guide for Information Technology Systems (National Institute of Standards and Technology, U.S. Department of Commerce, 2002) (Http://csrc.nist.gov/publications/nistpubs/800-30/sp800-30.pdf)*

How does the Agency align its current thinking on Risk-Based Approach with the approach described in the NIST Publication?

On behalf of Aventis Pharmaceuticals Inc. we appreciate the opportunity to comment on the draft guidance for Industry on Part 11, Electronic Records, Electronic Signatures – Scope and Application and are much obliged for your consideration.

Sincerely,

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