

Aventis Pasteur



21 December 2004

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

Re: Docket No. 2004D-0440; Draft Guidance for Industry on Computerized Systems Used in Clinical Trials; [69 Federal Register 59239, October 4, 2004]

Dear Sir/Madam,

Aventis Pasteur Inc. of Swiftwater, Pennsylvania thanks the Food and Drug Administration (FDA) for the opportunity to comment on the above-referenced draft guidance for industry entitled, "Computerized Systems Used in Clinical Trials." Aventis Pasteur Inc. is part of the Aventis Pasteur family of companies, which consists of the parent firm Aventis Pasteur SA, headquartered in Lyon, France, Aventis Pasteur Inc., and other subsidiaries (collectively Aventis Pasteur). In turn, Aventis Pasteur SA is a subsidiary of Aventis SA.

Aventis Pasteur is a world leader in vaccines and produces more than one billion doses of vaccines every year to immunize 400 million people around the world. Aventis Pasteur, in close consultation with the US public health establishment, including the FDA, and Centers for Disease Control and Prevention (CDC), strives to alleviate the suffering and death of vaccine-preventable diseases.

We offer the following comments for your consideration concerning the FDA's solicitation of responses as they apply to the Biologics (Vaccine) industry.

General Comments

1. The September 2004 draft guidance appreciably overlaps the August 2003 guidance "Part 11, Electronic Records; Electronic Signatures – Scope and Application" (hereafter referred to as the August 2003 Guidance). Examples of sections that are similar or largely duplicated between the two guidance documents include Section IV of the September 2004 draft guidance (compared

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with Section III of the August 2003 guidance), Section IX-A of the draft guidance (compared with Section III.C.3 of the August 2003 guidance), and Section XII of the draft guidance (compared to Section III.C.4 August 2003 guidance).

2. Some topics are presented in the September 2004 clinical trials guidance that conceivably represent valid overall recommendations in situations where electronic records or data are created, modified, maintained, archived, retrieved, or transmitted across a broader scope of regulated activities within the pharmaceutical industry. Some examples include draft guidance Sections V (Standard Operating Procedures), VI (Data Entry), X (System Controls), and XI (Training of Personnel). Information similar to that presented in these sections of the September 2004 draft guidance would be generally applicable to other areas such as research, development, manufacturing, testing, etc. but are not presented within the more general September 2003 Scope and Applications guidance.
3. In consideration of points 1 and 2 above, FDA may wish to consider future management of generally-applicable guidance information within the framework of a universal guidance document (such as a revision to the August 2003 Scope and Applications document) while maintaining separate guidance unique to specific areas of activity (for example a guidance related to the use of computerized systems in clinical trials).

Specific Comments

4. Lines 54-57: *“Although the primary focus of this guidance is on computerized systems used at clinical sites to collect data, the principles set forth may also be appropriate for computerized systems belonging to contract research organizations, data management centers, and sponsors.”* Aventis Pasteur notes that the reference to a *“primary focus”* while stating that the guidance *“...may also be applicable...”* to other situations is potentially confusing. Consider elimination of the statement to keep the scope of the guidance generally applicable to not only collection of data at clinical study sites but also to other aspects of electronic data or records management in support of clinical trials.
5. Lines 60-61: *“Computerized medical devices, diagnostic laboratory instruments, and instruments in analytical laboratories that are used in clinical trials are not the subject of this guidance.”* In many cases, these devices and systems are critical elements in the collection and management of electronic data and records in support of clinical trials. Consider elimination of this statement so as to not specifically exclude these systems and devices from the scope of the guidance.
6. Lines 78-81: *“For each study, we recommend that documentation identify what software and hardware are to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. We also recommend that this documentation be retained as part of the study*

records.” Aventis Pasteur agrees that the documentation identifying systems utilized during clinical trials should be maintained. We suggest that this be limited to the software and not include the hardware (e.g., servers). Records maintained in support of the system can be used to identify the system hardware.

7. Lines 137-146: *“We recommend that standard operating procedures (SOPs) pertinent to the use of the computerized system be available on site. We recommend that SOPs be established for the following: System Installation; Data Collection and Handling; System Maintenance; Data Backup, Recovery, and Contingency Plans; Security; Change Control; Alternative Recording Method.”* Aventis Pasteur agrees that SOPs appropriate to the system operation and maintenance be kept on site. Based on the system architecture (e.g., ASP), procedures other than general operation may not be appropriate for the site. This includes System Setup, Installation, Data Backup, Recovery, and Change Control. We suggest that this recommendation be modified to pertain only to SOPs that are needed at the site based on the system architecture and system activities to be performed at the site.
8. Lines 233-240: *“We recommend that controls be put in place to ensure that the system's date and time are correct. The ability to change the date or time should be limited to authorized personnel and such personnel should be notified if a system date or time discrepancy is detected. We recommend that someone always document changes to date or time. We do not expect documentation of time changes that systems make automatically to adjust to daylight savings time conventions. We also recommend that dates and times include the year, month, day, hour, and minute. The Agency encourages establishments to synchronize systems to the date and time provided by trusted third parties.”* Systems that are connected to a trusted third party for time synchronization can be automatically updated on a regular basis. Systems configured in this manner should not require that "someone always document changes to date or time." Aventis Pasteur suggests clarifying that documenting system time changes apply only when performed manually.
9. Lines 307-309: *“We recommend that a cumulative record be available that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. We recommend that the record be kept in the study documentation, accessible at the site.”* Personnel identification (user name/id and role) for many computerized systems is maintained within a system's data files / database. Aventis Pasteur suggests the guidance permit management of the specified 'cumulative record' via system security functionality and be limited to user name/id and access privileges. The appropriate procedures for maintaining user access in a timely fashion should be established to provide assurance of the access privileges at any point in time.
10. Lines 329-331: *“We recommend that systems documentation be readily available at the site where clinical trials are conducted and provide an overall description of the computerized*

systems and the relationships among hardware, software, and physical environment.” Aventis Pasteur agrees that the trial sites need to have adequate documentation to support system usage. Documentation beyond routine system usage information may be inappropriate for the site to possess (e.g., infrastructure relationships). These technical documents would provide minimal value to the clinical trial staff and may provide system information not appropriate for general users. We suggest removing the recommendation of providing technical documentation including hardware, software and physical relationship information.

Typographical Errors

- Line 20: Insert a period after “(FDA)”.
- Line 542: Insert a period at the end of the sentence.
- Line 563: Close parentheses and add a period at the end of the sentence.

On behalf of Aventis Pasteur Inc., we appreciate the opportunity to comment on this draft guidance and thank you for your consideration of these comments. Should you wish to discuss any of our comments further, please address inquiries directly to Denise L. Rieker, Manager, Regulatory Policy and Intelligence, by telephone at (570) 895-3465, or by email at denise.rieker@aventis.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Kenneth P. Guito".

Kenneth P. Guito
Global Head, Regulatory Policy and Intelligence

KPG/DLR/kh