

December 16, 2004



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

Re: Docket No. 04D-0440 Draft Guidance for Industry; Computerized Systems Used in Clinical Trials; Availability

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$3 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) October 4, 2004, *Federal Register* (FR) notice of draft guidance entitled *Computerized Systems Used in Clinical Trials*.

In general, Merck recommends that the FDA's final guidance document offer technical flexibility in order for companies to adapt to rapidly evolving computer technology and, where possible, the Agency should eliminate limitations that were necessitated in a paper recordkeeping environment. Two examples are:

- The physical location of electronic source records should be irrelevant to the Agency as long as appropriate access control, security, and audit trail functionality are applied to the system.
- The verification of accuracy and completeness of a 'certified copy' can be achieved through a validated computer program rather than through human review and signature (e.g., by using an "archive copy" maintained by a validated program).

Merck has also provided the following specific comments that address particular sections of the draft guidance document.

Specific Comments

Section III. General Principles

Line 76

“We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.”

Comment: It would be very difficult, if not impossible, for the sponsor to know prospectively all of the different systems for each study protocol that may be in use at each of the study sites involved in a clinical trial (e.g., systems used by hospitals, clinics, etc.), especially for large, multi-site studies. Therefore, we recommend that this requirement be deleted from the final guidance.

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.”

Comment: The FDA should anticipate that software documentation may be provided by a vendor or sponsor, that it is likely to be voluminous, that the same system(s) may be installed at many sites, and that storage of hardware and software documentation at the investigative site could be both burdensome and unnecessary due to the voluminous nature of most system documentation. We suggest replacing the first sentence starting on line 78 with the following:

“For each study, we recommend that documentation should be readily available to inspectors, but need not be physically located at each site.”

Lines 80 – 81

“We also recommend that this documentation be retained as part of the study records.”

Comment: It is unclear what ‘study records’ are being referred to in this sentence. We recommend that the FDA clarify the term “study records.”

Lines 107-109, Line 213-214 (Section VI. Data Entry)

“We recommend that audit trails or other security methods used to capture electronic record activities document who made the changes, when, and why the changes were made to the electronic record.”

Comment: Security methods should include process documentation, which are part of the control procedures, often explaining why changes were made to the electronic record (e.g., to correct a typographical error). The guidance should not mandate that the system capture why changes were made. The control procedures should be sufficient to explain why changes were made.

Section V. Standard Operating Procedures

Lines 137-146

Comment: Some of the information required by the FDA to be “available on site” in this section may be supplied by the vendor and may be proprietary. As written, we believe the FDA is requiring that the information must be available to inspectors at each site. However, this type of information may be housed by the sponsor (i.e., maintained by the sponsor and available to the inspector but not physically stored at the site). This is particularly true of systems downloaded to a site rather than physically installed at the site. Therefore, we recommend that the FDA change lines 137-138 to read:

“...(SOPs) pertinent to the use of the computerized system be available, as applicable at each site.”

Section VII. System Features

Lines 254-259

Please refer to subsection **A. Systems Used for Direct Entry of Data.**

Comment: The guidance should provide greater latitude than "prompts, flags, or other help features." The key provision is that users be able to identify out of range values, and to do so readily. The specific implementation of alerts or other features must make the best use of technology. We recommend that the Agency present the above suggestions (i.e., “prompts, flags, or other help features”) as examples of alerts but understand that companies may implement other features that accomplish the same functional goal.

Lines 258 - 259

“We recommend against the use of features that automatically enter data into a field when the field is bypassed.”

Comment: As written, the FDA is recommending against the use of system features that automatically enter data into a field when a field is bypassed (e.g., default values). It is likely that systems will use default values and in many cases, it is desirable (i.e., ease the flow of data entry). The change recommended below would allow “auto-filled” fields in some cases that may be appropriate (e.g., date field, etc.). We recommend changing Lines 258-259 to:

“We recommend that sponsors carefully consider the use of features that automatically enter data into a field when the field is bypassed.”

Line 268–271

“As explained in the Part 11 Scope and Application Guidance, FDA does not intend to object to required records that are archived in electronic format; nonelectronic media such as microfilm, microfiche, and paper;”

Comment: It is not clear if this section includes records at investigator sites, sponsors, or both. We request that the Agency provide further clarification.

Section VIII. System Security

Lines 313 - 315

“...we recommend that efforts be made to ensure that the study software be logically and physically isolated as necessary to preclude unintended interaction with nonstudy software.”

Comment: This section states that study software should be “logically and physically isolated” to prevent unintended interaction with non-study software. Merck recommends changing “and” to “or” since it may not be feasible to do both.

Lines 315-317

“If any of the software programs are changed, we recommend that the system be evaluated to determine the effect of the changes on logical security.”

Comment: The installation of other software on the investigator’s computer is outside of the control of the sponsor. If the system is validated prior to initial use in order to meet security needs and proven to not be affected by additional software installations, then no further evaluation should be required by the sponsor if the investigator installs other software on their computer. If the FDA includes the addition of any new software in its definition of “change,” then the sponsor would be required to re-evaluate the site each time new software is installed to their computer. Therefore, we request that the FDA limit the scope of this requirement to only include those changes that would negatively impact the security or the integrity of the programs or systems used in a study.

Section IX. System Dependability

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.”

Comment: We believe requiring this documentation to be readily available to inspectors and maintained at each site is an unnecessary and burdensome requirement because some systems documentation can be voluminous. We believe complying with this requirement may not be feasible because it would require sponsors to have all systems documentation readily available at the site. As previously stated in our comment regarding Lines 78-81, we believe the documentation should be available to inspectors, but not physically located at each site. Therefore, we recommend changing Line 329 to read:

“We recommend that systems documentation should be readily obtainable at the site upon request.”

Line 368

“There is documented evidence and justification that the system is fit for its intended use.”

Comment: Merck recommends that the FDA provide clarification in terms of what it is requiring by this sentence. It is not clear what is meant by the legacy system being “fit

for its intended use.” This statement is very close to the Agency’s definition of validation. If the expectation is that legacy systems should be validated, then it should be stated as such. If not, then please provide examples of alternative approaches.

Lines 386 - 392

Please refer to subsection **B. Off-the-Shelf Software**, paragraph 2.

Comment: For off-the-shelf systems, the guidance document requires a written design specification (either original validation or on-site vendor documents) describing what the software is intended to do. Design level documentation is proprietary. Therefore, it is unreasonable to expect vendors to provide a copy of this information or for FDA to require that each site store it. We believe the Agency should change this section to only require that sponsors document their requirements for the software and test it from a user perspective.

Also, it is not clear in this paragraph what is meant by “on-site vendor audit documents.”

Comment: If the intention of this section is to present vendor audit documents, then the requirement conflicts with longstanding FDA policy and would require sponsors to violate confidentiality agreements with vendors. Therefore, we recommend deleting the requirement to provide “on-site vendor audit documents.”

Lines 401-411

Please refer to subsection **B. Off-the-Shelf Software**, paragraph 4.

Comment: For off-the-shelf systems, it is not clear how the Agency can expect a sponsor to perform structural testing for a system in which they do not have the design or source code. Merck recommends changing the three bullets to remove the word “design” and replace it with the word “functional” and delete the requirement to structurally test the system (bullet 2). Also, we recommend that the Agency remove “how it is intended to do it” from the first bullet because the requirement is covered in design documentation, which we do not receive from vendors as it is proprietary information.

Section: Definitions

Line 565-568

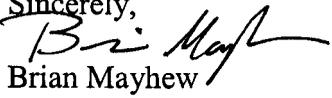
“Predicate Rule: This term refers to underlying requirements set forth in the Federal Food, Drug, and Cosmetic Act, the PHS Act, and FDA regulations (other than 21 CFR Part 11). Regulations governing good clinical practice and human subject protection can be found at 21 CFR parts 50, 56, 312, 511, and 812.”

Comment: We believe the FDA should accept future regulations as predicate even after this guidance is released. Presumably the FDA will issue other regulations regarding this topic in the future. Therefore, we recommend that the definition only include the first sentence, and strike the second sentence of the definition.

Summary

Merck appreciates the opportunity to provide input to the Agency on this guidance document. This is an area that will benefit from FDA's collaboration with industry. Our comments attempt to provide consistency and clarification of terms and provide the technical flexibility and operational efficiency necessary for the use of electronic recordkeeping systems for clinical trials. Additionally, by anticipating future enhancements to current technology and the availability of new technologies, the Agency can utilize technological innovations to remove the boundaries inherent in a paper recordkeeping environment.

If we can provide further assistance, or if you have any questions regarding our comments, please contact me at 301-941-1400.

Sincerely,

Brian Mayhew
Regulatory Policy Analyst
Regulatory Policy - Domestic