

Triangle PEERS
Research Triangle Park
North Carolina

16 December 2004

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

Re: Docket No. 2004D-0440

To Whom It May Concern:

Triangle PEERS is pleased to submit comments on the draft FDA Guidance for Industry: *Computerized Systems Used in Clinical Trials*. Triangle PEERS (**P**art **E**leven & **E**lectronic **R**ecords **S**takeholders) is an association based in Research Triangle Park, North Carolina, whose membership represents over forty organizations, including pharmaceutical companies, clinical research organizations, academic research organizations, validation and IT systems consultants, and technology vendors. PEERS members possess expertise in a variety of perspectives such as technology, process engineering, quality assurance, regulatory affairs, data collection and management, legal, and data security. PEERS members focus primarily on the practical implementation of regulations, guidance and standards pertaining to electronic records, including 21 CFR Part 11, particularly as this applies to Good Clinical Practices (GCPs) in the conduct of clinical trials.

PEERS applauds the FDA's efforts to improve the FDA Guidance, *Computerized Systems Used in Clinical Trials* (April 1999). The additional sections on the level of validation, audit trails, change control, copying of records based on the need to meet predicate rule requirements, justified and documented risk assessments, and determination of the potential effect on data quality and record integrity are appreciated. The FDA is also to be commended for deleting sections on electronic signatures at the start of a data entry session, durable media, calculation of local time stamps, inappropriate data tags, and the requirement to retain all versions of application software.

PEERS is pleased that the draft guidance is now aligned with the FDA Guidance for Industry, *Scope and Application* (September 2003). This provides greater consistency for companies that deal with areas across all GXPs.

The draft guidance is also helpful since it specifically focuses on the expectations for computerized systems used in clinical trials. It is helpful that the FDA has provided some citations to predicate rules regarding general record and responsibility requirements. However, if 21 CFR Part 11 undergoes significant revision or is revoked, the draft guidance alone would be insufficient to address GCP predicate rule concerns. As previously noted in PEERS comments to the FDA Docket 2004N-0133, the regulations for the conduct of clinical trials do not provide adequate direction for electronic records or validation.

PEERS members appreciate the flexibility in approach afforded by this document. This document definitely focuses more on what is expected and not on how these expectations are implemented.

The specific comments of PEERS follow, organized sequentially by the sections of the draft guidance.

Section I. Introduction

PEERS recommends that the FDA establish the scope and context of this draft guidance for all computerized systems used in clinical trials. As now written, the draft guidance talks about clinical data (possibly the CRF-type data), but it does not indicate whether it applies to other types of systems that may hold regulated electronic records (e.g., protocol, drug accountability, IRB meeting minutes, investigator financial disclosure records, adverse event reports). These records, if kept electronically, still fall under the predicate rules and are subject to Part 11 yet the draft guidance is unclear whether they are in scope.

The draft guidance neither addresses the concept of implied records nor other areas where computers may be used to control processing (e.g., assignment of treatment groups per randomization code, control of or acquisition from instruments during Phase 1 trials). Implied records occur when predicate rules require an activity (such as sponsors ensuring proper monitoring per 21 CFR 312.50) but make no mention of records; however, records may be expected as evidence that the activity occurred. As a result, the GCP industry is again left without specific guidance for many computer systems used in clinical trials other than the predicate rules and the *Scope and Application* guidance. At a minimum, PEERS requests the FDA to address the implied records issue.

To clarify further the scope of the draft guidance, PEERS recommends that the FDA use consistent terminology to reference the mix of data, records, and documents from computerized systems used in clinical trials. In lines 18-24, PEERS suggests that the phrase “clinical trial records” be substituted as follows (proposed changes in bold) and appropriately defined:

This document provides guidance about computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit **clinical trial records** required to be maintained and/or submitted to the Food and Drug Administration (FDA). These **clinical trial records** form the basis for

the Agency's decisions regarding the safety and effectiveness of new human ~~and animal~~ drugs, biological products, medical devices, and certain food and color additives. Because the ~~data~~ **clinical trial records** have broad public health significance, they are expected to be of the highest quality and integrity. This guidance document addresses long-standing FDA regulations concerning clinical trial records.

Section III. General Principles

General principle #7 (lines 97-109) recommends that audit trails or other security methods capture who made changes, when, and why changes were made to electronic records. Documenting the reason for change ("why") in an audit trail would not be required unless so directed by predicate rules. PEERS notes that GCP predicate rules do not require a reason for change. Typically, an audit trail would contain a high-level characterization (e.g., create, modify, delete) of the record activity event but this would not include any expanded justification to explain the reason for change. PEERS recommends that FDA delete the word "why" in line 109. See also lines 214-215 for the same issue.

General principle #8 (lines 110-111) states that information regarding each individual subject should be "attributable" to that subject. PEERS recommends that the FDA rephrase this to avoid any confusion with the concept of Attributable Data. As defined in the draft guidance, attributable data includes traceability to the individuals responsible for observing and recording the data. PEERS recommends that FDA consider clarifying principle #8 as follows (proposed changes in bold): "We recommend that data be retrievable in such a fashion that all information regarding each individual subject in a study is **associated** with that subject."

Section VI.A. Computer Access Controls

Lines 163-165 appear to provide guidance on minimizing the risk of misuse or misappropriation of passwords. PEERS believes this should be broadened to include all types of access methods and allow for any type of control that might be used. Additionally, PEERS believes the recommendation to change passwords at established intervals should be expanded to provide examples of the factors that might be considered when establishing the frequency of change. Systems with "strong" password enforcement (as indicated by password length, mixture of characters used, capitalization sensitivity, etc.) or those used with lower risk records may not require the same change interval as those with "weak" passwords or higher risk records. Thus, PEERS recommends that lines 165-166 (starting with "We also recommend ...") be replaced with the following:

We also recommend that controls be put into place to minimize the risk of misuse or misappropriation of controlled access methods. An example could be the periodic change of passwords or other access keys. If passwords are utilized as a control, we recommend that the established

interval for password changes be based on a documented risk assessment and a determination of the potential effect on data quality and record integrity. This assessment should take into account the various factors that can affect the frequency of change, such as strength of password, physical security surrounding the system, risk to data integrity or patient safety, and the strength of other system-based controls.

Section VI. B. Audit Trails or other Security Measures

PEERS appreciates FDA's guidance in lines 206-208 regarding the elements to consider when evaluating risk: "Firms should determine and document the need for audit trails based on a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities."

The examples for tracking changes to electronic records in lines 217-229 are helpful but PEERS recommends that the FDA move lines 228-229 since this is not a method for tracking changes. Lines 228-229 logically follow after current line 215 as the last sentence of that paragraph. PEERS recommends that the FDA slightly amend these lines to read (proposed changes in bold): "**We recommend that controls prevent** unauthorized personnel from creating, modifying, or deleting electronic records or the data contained therein."

In lieu of current lines 228-229, PEERS further recommends that FDA add the example of maintaining a procedurally required manual log of changes to electronic records (with who, what, when, signed/dated), which might be appropriate and acceptable in certain circumstances.

Section VII. B. Retrieval of Data and Record Retention

PEERS applauds the FDA's practical approach to record retention and study reconstruction. The draft guidance no longer expects industry to reprocess data or rerun software. Instead, the draft guidance indicates it would be sufficient to have an understanding of what software was used, how, for what purpose, in what environment, what it did, and how it was proven (reconstruction of process via system documentation). This is a reasonable approach.

PEERS recommends that the FDA delete the references to XML and SGML in line 271 as standard electronic file formats. XML and SGML are not electronic file formats; instead XML and SGML are formal descriptions of the content of a file and indicate how that content should be structured.

Section IX. System Dependability

Lines 353-354 indicate that "Clinical investigators are not generally responsible for validation unless they originated or modified software." PEERS requests that the FDA amplify the responsibility of clinical investigators for the validation and documentation of their own computerized systems used in the clinical environment for source data. PEERS members have found that clinical

investigators may not be fully aware of Part 11 controls for their own computerized systems, thus potentially putting clinical study data for Sponsors at risk. The distinction should be made that Sponsors are responsible for the validation and documentation of computerized systems supplied by the Sponsor to the clinical trial environment.

Section IX. A. Legacy Systems

FDA reiterates its position that it will not enforce Part 11 if a legacy system meets certain criteria, including all current predicate rule requirements; if a legacy system was changed and does not meet current predicate rule requirements, then Part 11 controls should be put in place. The net effect is that all systems - new systems, unchanged legacy systems, changed legacy systems - must meet predicate rule requirements. The continued use of the term “legacy systems” creates confusion. PEERS suggests that the entire legacy systems section be changed to state that there is no distinction, and that all systems must meet applicable predicate rule requirements.

Alternatively, if the concept of legacy systems is retained, PEERS recommends that the FDA delete Section IX.A. altogether because it is already addressed in the *Scope and Application* Guidance. Instead of reiterating the content, the FDA should reference the *Scope and Application* Guidance.

Section IX. B. Off-the-Shelf Software

In this section, the FDA recommends that the Sponsor or CRO have design specifications for off-the-shelf software in order to conduct functional testing. This is unrealistic because the Sponsor or CRO would typically not have access to the vendor’s proprietary design specifications against which to perform functional testing. Instead, purchasers of off-the-shelf software typically conduct a performance qualification (also known as User Acceptance Testing) against a written requirements specification document followed by completion of an installation qualification.

Accordingly, PEERS recommends that the FDA revise this section to reflect the accurate use and meaning of technical validation terms. To achieve this, PEERS suggests that the FDA delete the word “functional” in line 389, substitute the word “requirements” for “design” in lines 404-409, and delete the phrase “including both structural and functional analysis” in lines 406-407. These changes would then reflect practical best practices for off-the-shelf software.

Section IX. C. Change Control

PEERS appreciates the information on change control, because it emphasizes the importance of evaluating the effects of any changes and taking appropriate validation action.

Section X. System Controls

In lines 432-434 on software version control, the FDA recommends measures to ensure that the versions of software used reflect the versions stated in the systems documentation. Would the FDA also want to make sure that the software version in use is the same as the version documented in the study records, which industry is instructed to maintain in lines 76-81? PEERS recommends adding the phrase “and study records” to this sentence for clarity, as follows (proposed changes in bold): “We recommend that measures be put in place to ensure that versions of software used to generate, collect, maintain, and transmit data are the versions that are stated in the systems documentation **and study records.**”

PEERS recommends that the FDA clarify lines 443-445 as follows (proposed changes in bold): “When **using electronic records**, the Agency recommends that backup and recovery procedures be outlined clearly in SOPs and be sufficient to protect against **the risk of** data loss.”

Section XI. Training of Personnel

Documentation of education, training, and experience is generally required by the predicate rules. However, Part 11 was the first instance in which training, education, and experience specifically referenced those IT professionals who maintain and develop computerized systems, not just the system users. As written, Section XI focuses exclusively on the system users and their training. PEERS recommends that line 470 be amended to amplify the requirement of education, training, and experience for users, developers, and maintainers of computerized systems used in clinical trials.

Section XIII. Certification of Electronic Signatures

This section fails to directly state the responsibility of clinical investigators to submit an electronic signature certification. PEERS requests FDA to clarify whether sponsors can certify on behalf of clinical investigators.

Definitions: Software Validation

The definition of Software Validation in the draft guidance (lines 566-570) does not match the definition of Software Validation in the FDA *Glossary of Computerized System and Software Development Terminology*, August 1995, i.e., “(NBS) Determination of the correctness of the final program or software produced from a development project with respect to the user needs and requirements.” PEERS encourages the FDA to adopt and utilize a consistent definition for computer system validation. As such, PEERS reiterates its comments submitted earlier to the FDA for docket 2004N-0133 (notice of public meeting) regarding the need for a consistent definition for computer system validation:

“The predicate rules for GLP and GMP contain regulations that can be interpreted to cover computer systems validation; in contrast, GCP

predicate rules do not mention computer systems, yet computer systems are used for key activities in clinical trials. Since computer system validation is not defined adequately in the predicate rules and can be interpreted in various ways, PEERS recommends that the definition for computer system validation be standardized, as proposed below. To avoid further confusion, PEERS also recommends that the major deliverables of validation – predetermined requirements, design specifications, testing against those requirements and specifications, and change control to maintain the computer system in a validated state – be listed with the definition.

Computer System Validation: The ongoing process of establishing documented evidence that provides a high degree of assurance that a computerized system will consistently perform according to its predetermined requirements and quality attributes. This includes procedures, requirements and specifications, testing, and change control.”

Definitions: Certified Copy

Although a definition for certified copy is provided, PEERS notes that the draft guidance fails to mention certified copies in relevant sections such as transmitting data and copying electronic records for regulatory inspections .

In footnote 4 to the word “original” in line 50, the FDA indicates it will allow for retention of certified copies, as opposed to originals. In the past, the clinical research industry has generally understood the term ‘original records’ to mean “not a copy.” The FDA is expanding the definition of original records to include “certified copies” and PEERS members are in agreement with this concept, particularly since many patient medical records are becoming electronic images through the process of scanning paper originals at many of the sites where clinical trials are being conducted. However, the use of certified copies within an electronic environment raises questions that the FDA should resolve.

First, the definition in lines 537-538 and the referenced Compliance Policy Guide #7150.13, Use of Microfiche , indicate a certified copy is verified to be an exact copy by application of a dated signature. This concept makes sense in the context of a paper copy. An electronic record can be printed, the paper verified against the electronic version before deleting the electronic version, and then the printout signed with a handwritten signature. But if the copy is electronic, does FDA expect the verification of the copy to be done via an electronic signature? PEERS points out that this is unclear and requests that the FDA address whether electronic copies of electronic records transmitted from a clinical investigator to a CRO / Sponsor or electronic copies provided during a regulatory inspection need to be certified copies, i.e., verified and signed either by electronic or handwritten signatures.

The process of verifying certified copies of electronic records also needs to be addressed. Typically, when transferring records to electronic storage media (e.g., CD-ROM), every single record is not necessarily “certified” as being true and accurate; instead, the electronic storage media as a whole is reviewed for accuracy and completeness to verify that the scanning/archiving process meets certain standards of quality. Similarly, Medical Record Departments scan paper documents and certify the accuracy of the process for legibility and completeness, but generally do not certify the integrity of the information contained within each copy. Likewise, patient diary entries may be captured on a PDA with a subsequent upload to a server, essentially creating a copy, so that the entry on the PDA does not need to be retained. In each of these examples, what is required to meet the definition of Certified Copy in lines 537-538? The requirement to sign and date every individual record of a certified copy may seem reasonable, but it is not practical in today’s computerized environment where the goals are to become paperless and more efficient.

As a result, PEERS recommends that the FDA address whether (1) an electronic algorithm (for example, a checksum) to verify accuracy of transfer and/or (2) a validated automated process (proving everything is copied completely, accurately, is mapped correctly, etc.) would be acceptable methods to certify electronic copies, as long as there is documentation to prove the process works and is controlled.

Finally, by referencing the Compliance Policy Guide #7150.13, Use of Microfiche, in lines 50 and 559, the draft guidance attempts to associate the use of microfiche (from the 1980s) with the process of scanning records in today’s technological environment. When item #3 in this Compliance Policy Guide is applied to scanned images, it would not allow for the original paper record to be destroyed even if the scanned image is “certified.” Therefore, when the FDA suggests in lines 556-559 that original documents could be replaced by certified copies, no benefit could be achieved from scanned images since changes, additions, alterations to the original record cannot be revealed/noted as stated in item #3 of the Compliance Policy Guide. This appears to run counter to FDA’s intent. PEERS recommends that the Compliance Policy Guide be updated to reflect current technology.

Definitions: Electronic Signatures

PEERS notes that electronic signatures are included in the Definitions section, but are rarely mentioned in the draft guidance.

eCRFs and Patient Diaries

Even though the definitions for Electronic Case Report Form (eCRF) and Electronic Patient Diary (“ePD”) in the FDA Guidance, *Computerized Systems Used in Clinical Trials* (April 1999) were deleted, the issue of the clinical investigator’s maintenance of data from eCRFs and ePD still exists. PEERS requests that the FDA clarify in the final guidance that a clinical investigator’s

contemporaneous access to eCRF and ePD data during a clinical study meets the predicate rule expectations for maintaining the data.

In closing, Triangle PEERS appreciates the opportunity to comment on the draft FDA Guidance, *Computerized Systems Used in Clinical Trials*.

Sincerely,

Triangle PEERS
Research Triangle Park
North Carolina
<http://peers.onsphere.com>