American Red Cross

Together, we can save a life

December 21, 2001

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

RE: Draft Guidance for Industry: 21 CFR Part 11; Electronic Records; Electronic Signatures Validation [66 FR 48886, September 24, 2001; Docket # 00D-1538]; and Draft Guidance for Industry: 21 CFR Part 11; Electronic Records; Electronic Signatures Glossary of Terms [66 FR 48886, September 24, 2001; Docket # 00N-1543]

Dear Docket Officer:

This letter is to provide public comments on behalf of the American Red Cross (ARC or Red Cross) concerning the Food and Drug Administration's (FDA or Agency) two draft guidances: 21 CFR Part 11; Electronic Records; Electronic Signatures Validation (draft Validation Guidance) and Glossary of Terms (draft Glossary).

The Red Cross, through its 36 Blood Services regions, supplies approximately half of the nation's blood for transfusion needs. The blood donated by Red Cross volunteers is also recovered and processed or fractionated into plasma derivatives. Red Cross is also a large supplier of human allograft tissue.

The Red Cross is committed to the safety of our donors, our patients, and the public we serve. Thus, the Red Cross fully supports these two guidances, which give further assistance in interpreting the regulatory requirements.

Our main points can be summarized as follows:

- The draft Validation Guidance contains recommendations aimed at more general validation practices, rather than targeting only those specifically pertaining to Part 11. We do not object to the concept of broader, more comprehensive validation guidance. Indeed, we encourage FDA to pursue development of one. However, to streamline

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the Part 11 draft Validation Guidance, we encourage FDA to eliminate validation requirements that do not pertain specifically to Part 11.

- ARC recommends that FDA issue the planned "Scope" guidance, prior to closing the public comment period on the draft Validation Guidance and Glossary. The anticipated "Scope" Guidance may include information and recommendations that impact the Validation Guidance or Glossary that we cannot expect at this time. If FDA does not issue a separate "Scope" Guidance, we urge FDA to clearly indicate the validation steps covered in the final Validation Guidance.

- The Red Cross believes FDA did not intend the term "should," to mean, "must" in every instance it is used to describe a validation activity. Rather, we believe there are some activities that the user "should consider" or "should assess" to determine if it is appropriate to perform the activity. In the attachment, we have noted where clarification of FDA's intentions would be beneficial.

- ARC recommends changing the approach to providing a Glossary as a separate guidance. Instead, we urge FDA to include a Glossary in each individual guidance. This will eliminate the need for FDA to update, and for users to implement, two guidances whenever a major change is needed in an individual guidance or when an industry practice is modified.

The Red Cross appreciates the Agency's efforts to clarify and communicate their expectations regarding Part 11 and this opportunity to provide public comments on these important draft guidances. If you have any further questions or require follow-up, please contact Anita Ducca, Director, Regulatory Affairs at 703-312-5601 (phone), 703-312-5816 (fax) or DuccaA@usa.redcross.org (e-mail).

Sincerely,

Gary D. Dolch, Ph.D.
Senior Vice President, Quality and Regulatory Affairs

Attachment

Comments by
The American Red Cross
On the
Draft Guidances for Industry: 21 CFR Part 11; Electronic Records; Electronic Signatures, Validation
[66 FR 48886 September 24, 2001 Docket # 00D-1538];
and
Electronic Records; Electronic Signatures, Glossary of Terms
[66 FR 48886 September 24, 2001 Docket # 00N-1543]

The American Red Cross (ARC or Red Cross) is pleased to provide these comments to the Food and Drug Administration (FDA) the two draft guidances: 21 CFR Part 11; Electronic Records; Electronic Signatures Validation (draft Validation Guidance) and Glossary of Terms (draft Glossary). These comments discuss certain general issues we'd like to bring to FDA's attention, followed by section comments.

General Comments

i. Comprehensive Validation Guidance

Throughout the draft Validation Guidance, FDA touches upon validation practices at great length. However, the draft goes beyond what we believe is appropriate for a guidance pertaining to Part 11. ARC does not object to receiving validation guidance, but using this approach, i.e., adding general validation guidance to a Part 11 specific guidance, falls short of providing adequate guidance on either. What is needed to cover Part 11 is somewhat confused by intermingling general validation guidance within it, and the general validation aspects are incompletely covered.

ARC would welcome a separate, comprehensive software validation guidance and encourages FDA to prepare one. For the Part 11 draft under review, ARC requests that FDA eliminate references to validation practices that do not pertain specifically to Part 11. Should FDA issue a separate validation guidance, end users will find themselves working between two guidances, which may either conflict or overlap with each other, unless the general validation recommendations are removed from the draft Part 11 guidance. Further, FDA will find that it must modify and update two guidances, rather than one, as changes in industry practices indicate. (Examples where the draft Validation Guidance references practices not pertaining to Part 11 will be given throughout the remainder of our comments.)

ii. Scope of Coverage

A second concern involves future guidances. It is our understanding that the draft Validation Guidance and Glossary are the first two of a number of Part 11 guidances. One of the additional, subsequent guidances will define the "Scope" of coverage. ARC is concerned that the Scope Guidance, and associated public comments, may have a significant impact, or result in changes to these two draft guidances documents, that cannot be anticipated at this time. Thus, we may miss an opportunity to fully evaluate and provide comprehensive input on all the Part 11guidances.

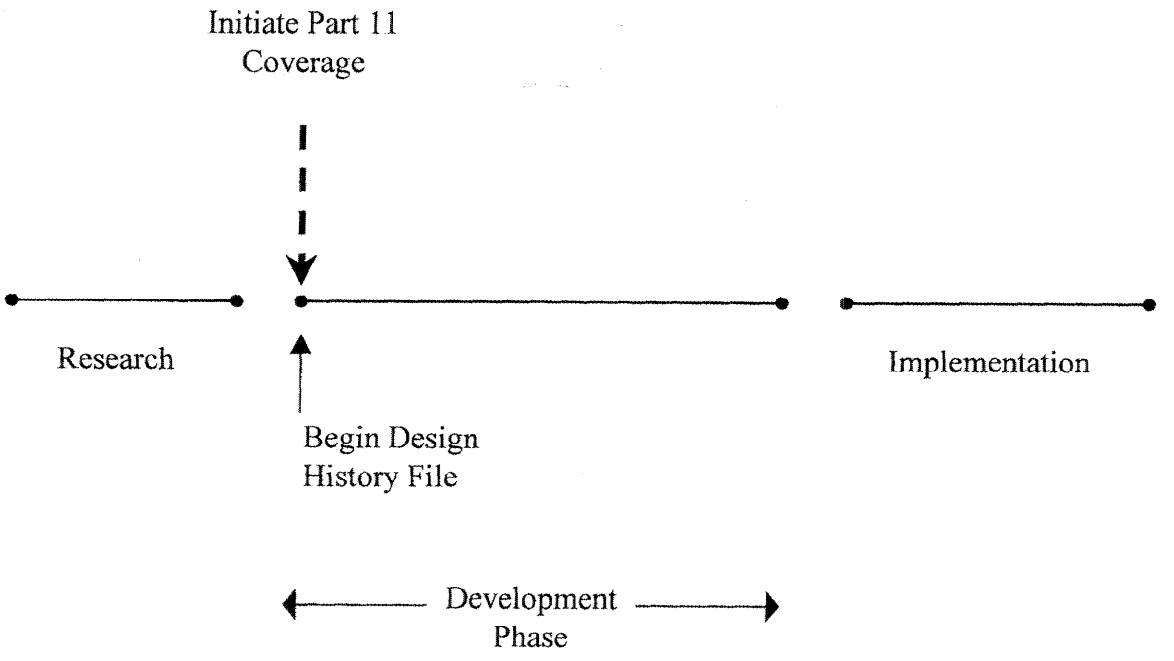
ARC recommends that FDA publish its draft Part 11 Scope Guidance as quickly as possible and allow the public comment period for the draft Validation Guidance and Glossary to remain open at least until after the comment period for the Scope Guidance closes. It is even more preferable for FDA to review the public comments and finalize the Scope Guidance before closing the comment period on any of the remaining guidances. With all dockets remaining open until after completion of the Scope Guidance, we will be better able to evaluate the interrelationship of all the guidances and provide comments that will have greater utility to FDA and to the regulated community.

If FDA does not intend to issue a "Scope" guidance, the ARC recommends that FDA specify in these guidances, the lifecycle of an electronic record and how that lifecycle is expected to intertwine with a product lifecycle. Initial meetings and discussions of potential product needs and options, for example, should not be considered subject to either Part 11 or the accompanying guidances, particularly when documentation requirements are considered. Without such clarification, blood establishments may find it necessary to go to extensive lengths to develop documentation for projects that never materialize into viable products. Such clarification will also help us direct product development resources in the most appropriate fashion.

ARC notes that there are three general phases in the product development process: 1) research phase, 2) product development process, and 3) implementation/installation. We believe an appropriate starting point for Part 11 coverage, particularly with respect to the validation requirements, is at the start of the design history file i.e., when the design input begins. In particular, ARC recommends starting coverage after the research phase, to help avoid unnecessary validation efforts of products that undergo research as we're considering concepts, customer requirements, and feasibility.

The chart on the following page provides a graphic representation of this concept.

Recommended Part 11 Coverage
Of the Product Development Process



iii. Clarify Expectations

Before finalizing the draft Validation Guidance, we urge FDA to clarify and revise the language to indicate their expectations for adhering to the guidance. Specifically, the Red Cross interprets the term "should" used throughout the draft Validation Guidance to mean that the activity is advisable or that users are expected to evaluate whether the action is applicable. However, "should" does not mean the action is required in every instance. We point this out since the term "should" might be subject to alternative interpretations, particularly during an FDA investigation, i.e., that "should" perform an action equates to "must" perform the action.

This interpretation is based on our experience and that of software engineering generally, where there are often cases when the actions that the user "should" perform are either unnecessary or an alternative produces an equivalent desirable result. In these instances, we would hope that our validation practices would be suitable. Although the beginning

of the draft Validation Guidance indicates that alternatives are acceptable[1] we urge FDA to match the language throughout the draft Guidance to actual validation practice and FDA expectations.

GUIDANCE FOR INDUSTRY: 21 CFR PART 11; ELECTRONIC SIGNATURES: ELECTRONIC RECORDS; ELECTRONIC SIGNATURES VALIDATION

2.1 Applicability

This section discusses "predicate rules" which fall into several categories. Examples of such categories include "pre-clinical research." ARC believes it is inappropriate to include this item as an example and recommends its deletion from the final guidance. Pre-clinical research pertains to the very earliest stages of research and development, and ARC believes that, as with the research phase of any product's development, coverage of products where very initial evaluations are being conducted is not warranted. (See general comments above under *ii. Scope of Coverage.*)

5.1 System Requirements Specifications

This section indicates that that the firm should be able to trace the user needs and intended uses to "system design requirements and specifications."

However, for off-the-shelf software, the system design requirements and specifications are not always available to end users since vendors typically regard this as proprietary information. Section 6 of the draft guidance acknowledges that they are not always available, but section 5.1 does not appear to have an equivalent recognition. ARC requests that FDA clarify in section 5.1, as well as in section 6, that the agency understands that for off-the-shelf software, this information is desirable but not required.

This section also contains references to expectations that may be appropriate validation practices but are not applicable to Part 11. The term "system performance" is one such item, i.e., generic to validation, but unrelated to Part 11. If FDA has an alternative use in mind, we recommend either changing the term, for example, to "system functionality," or developing a definition of "system performance" that is appropriate for application to Part 11.

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[1] The draft guidance includes the FDA statement: "....An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations."

The second bullet of this section, which describes "Scalability", is another example of a requirement that is appropriate as a validation practice, but does not pertain to Part 11. We encourage FDA to eliminate the reference to Scalability and include only guidance pertaining to Part 11 in the final document.

5.2 Documentation of Validation Activity

As noted earlier, ARC does not object to having validation guidance of a more general comprehensive nature. However, the statements in section 5.2 are more appropriately included in the broader validation guidance than in this Part 11 validation guidance.

This section indicates to all users that "Validation documentation ***should*** include a ***validation plan***." [emphasis added] ARC agrees with FDA's intentions. However, we have found that in many instances the validation documentation may be contained in documents other than a "validation plan," such as a test plan, a management plan, or in documentation accompanying an acceptance test. ARC requests that FDA revise this section's wording to indicate that users may use alternative approaches as long as validation is accomplished.

5.2.1 Validation Plan

This section provides a further description of the "validation plan" including a statement that it is a "**strategic document** that should state **what is to be done, the scope of approach, the schedule of validation activities, and tasks to be performed**." [emphasis added]

Similar to our comments on section 5.2 directly above, we urge FDA to acknowledge that a comprehensive 'validation plan" with the level of detail implied by this recommendation may not be necessary in all instances. ARC recommends that FDA indicate clearly that users may evaluate the particular application under development on a case by case basis. Additionally, we request that FDA indicate there is flexibility to develop a validation plan with a level of complexity that is commensurate with the level of validation effort that is needed.

ARC also wishes to point out that we interpret the statement "the schedule of validation activities" to mean that the steps and procedures included in the validation effort will be ordered in an appropriate sequence. However, one possible interpretation of this phrase is that FDA expects users to include specific dates for completion.

We have often found that including specific dates in such plans will only result in modifications due to unanticipated test results, the need to locate additional staff expertise, or other events that take place during the validation process. Date changes are also likely to require extensive documentation, potentially adding further delays to the

validation efforts. If FDA intended users to take action different from our interpretation, that is, to develop plans that lock in dates, we urge FDA to modify the draft guidance. We recommend that FDA indicate that a schedule developed as a sequence of events, listed in their appropriate order, will be acceptable without including completion dates.

5.2.2 Validation Procedures

ARC requests clarification of the term "Validation Procedures". ARC's interpretation of this phrase is that FDA is referring to what is most often called a "Validation Protocol". If so, we recommend the standard industry term of Validation Protocol be used in place of "Validation Procedures". We also request this clarification since the term "Validation Procedures" is sometimes interpreted to mean operating procedures or test procedures, which are actually only a part of the validation protocol.

ARC also recommends rewording of the 2nd sentence in this section. Specifically, we request that FDA insert the words "or reference" into the second sentence so that it would read: "It should describe ***or reference*** the computer system configuration…". Frequently, the documentation for the computer system configuration is located in a separate pre-existing document, and this rephrasing will allow us to retain the appropriate information in the same location.

5.4.1 Dynamic Testing

ARC notes that the first bullet under this section indicates that "Test conditions ***should*** extend to boundary values …". [emphasis added] However, not all of the examples included in the remainder of the list will always be included in the test conditions for all the software. Thus, ARC urges FDA to clarify that they expect users to ***consider*** extending such efforts to all the conditions noted, but are not expected to ***include*** all conditions if they are not applicable.

In the third bullet under "Live user-site tests," the draft indicates that "Testing should cover continuous operations for a sufficient time to allow the system to encounter a wide spectrum of conditions and events in an effort to detect any latent faults…" ARC finds FDA's intent in including this sentence ambiguous. We believe that the previous sentence, which indicates that this testing is done under "actual operating conditions" provides more than adequate direction to end users about the appropriate testing conditions. Thus, we recommend deletion of the last sentence under this bullet to avoid potential confusion.

5.4.2 Software testing should include:

ARC recommends that FDA modify the title of this section to eliminate the phrase "should include:" so that the title will read "Software testing." This modification will allow the user the flexibility to determine the appropriate testing and thereby have the ability to make decisions that optimally target the software's testing needs.

5.4.3 How test results should be expressed

ARC recommends revision of the second sentence under this section to read "Subsequent review and independent evaluation of the quantified test results should be considered and performed where applicable." We believe this change will indicate that there may be instances where an independent review is not only possible but also advisable.

5.5 Static Verification Techniques

ARC recommends moving the section on Static Verification Techniques to a position earlier in the guidance prior to finalization, preferably to a position before the section on Dynamic Testing. This change will help foster an understanding that static analyses may need to occur earlier in the validation process.

6.1 Commercial Off-The-Shelf Software

ARC concurs with the statements in this section. In particular, we agree with FDA's statements that:

> The end user is responsible for a program's suitability as used in the regulatory environment. However, the end user's validation approach for off-the-shelf software is somewhat different from what the developer does because the source code and development documentation are not usually available to the end user. End users should validate any program macros and other customizations that they prepare.

FDA has clearly indicated that the end user is responsible for a program's suitability for the particular use in their own facility's application. FDA also acknowledges that the end user is allowed to make this determination if the vendor does not make available the off-the-shelf source code and development documentation. We wish to note that we agree with both policies, since they have bearing on other requirements and clarifications within the draft.

6.1.1 End User Requirements Specifications

The draft guidance states "If possible, the end user should obtain a copy of the developer's requirements specifications for comparison". While we agree that it is desirable to have this information, our experience has been that the developer will not routinely release their requirements specifications. Additionally, it is more important for the end user to define their own requirements. Thus, we suggest that FDA emphasize the need for the user to identify their own requirements, over obtaining the developer's requirements specifications for comparison.

It is also unclear from the guidance the extent of the efforts FDA expects end users to make to obtain the developer's requirements specifications, or to document those efforts. ARC assumes that FDA will agree with us that extensive efforts to locate and document the developers' requirements specifications are not warranted, and should not be expected. We also urge FDA to highlight in future FDA staff inspection guidance and training, the greater value of an end user's other validation efforts.

6.1.2 and 6.1.3 Software Structural Integrity and Functional Testing of Software

First, ARC wishes to point out that we agree that "Software Structural Integrity" (6.1.2) and "Functional Testing of Software" (6.1.3) are appropriately considered as part of the software development. However, we recommend revising the draft guidance to indicate that when this testing is appropriate, it may be performed and documented separately from the validation plan.

We also recommend that FDA indicate that the end user may create a reference or link to the location of the documentation by describing in the validation plan where full documentation of structural and functional testing can be found. We believe it should be acceptable to incorporate such testing documentation into the acquisition documentation.

6.1.2 Software Structural Integrity

The Software Structural Integrity section states that "...end users should infer the adequacy of software structural integrity by ***doing all*** of the following..." [emphasis added]

ARC agrees that end users should study and evaluate the points that FDA has noted, including the research into the program's use history and the supplier's software development activities. However, we do not believe that all these recommendations will need to be performed in <u>all</u> cases.

ARC encourages FDA to clearly indicate that it is not mandatory to perform these steps in every case. We further suggest revising the language to read "infer the structural integrity by ***evaluating all*** of the following ***and performing the next steps where appropriate***..." or by deleting the word "all" so that this sentence would read "...infer the structural integrity by doing the following..." This revision will help ensure that the blood establishment actions will focus actions on those that are considered necessary for testing the structural integrity, and avoid that do not have a value added to the final product.

6.1.3 Functional Testing of Software

ARC agrees with the points made in this section. However, we believe that the last sentence does not provide additional information or contribute to what has already been discussed. FDA's expectations for end User Requirements and Software are fully defined by the recommendations in 6.1.1 and 6.1.2. Thus, we recommend elimination of the last sentence under Functional Testing.

6.2.1 Internet Validation

ARC agrees that the draft guidance should contain a reference to Internet Validation and, for the most part, this section is appropriate for Part 11 purposes. However, ARC strongly recommends deletion of the measures stated in the second bullet, which currently reads:

> Delivery acknowledgements such as receipts or separate confirmations executed apart form the Internet (e.g. via fax or voice lines).

At best, this requirement is extremely impractical. The Internet is the most advanced form of technological communication. Any other, including fax or telephone, is slower speed, more cumbersome, and, even after validation, more likely to result in errors, than the Internet.

In effect, this requirement would eliminate the improvements made by the Internet, and ARC has not been able to identify a benefit or justification for the requirement.

GUIDANCE FOR INDUSTRY: 21 CFR PART 11; ELECTRONIC SIGNATURES: GLOSSARY OF TERMS

ARC's single comment on the draft Glossary is that we encourage FDA to incorporate a Glossary, perhaps as an appendix, into each individual guidance, rather than include a Glossary as a separate guidance document. If prepared and issued separately, FDA will need to update and revise the separate Glossary each time an individual guidance is revised. Likewise, users will be required to evaluate and implement two guidances each time an update is made. We believe it will be more efficient to develop and revise the Glossary as part of the individual guidances.