From: Beers Block, Patricia on behalf of OC GCP Questions
Sent: Monday, December 19, 2005 10:25 AM
To: [redacted]
Subject: RE: Source Documents in Clinical Studies

Dear [redacted],

We anticipate that paperless studies will be more common as computers/specialized software becomes available for use in clinical settings. The regulations governing the conduct of clinical trials (e.g., 21 CFR 312, 812, etc.) require that clinical investigators prepare and maintain adequate, complete and (with devices) contemporaneous case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as control (in the case of drug studies), and administered the investigational device (in the case of device studies). Based on 21 CFR Part 11 (Electronic Records and Electronic Signatures), electronic records can be used in lieu of paper provided the computerized system/software are compliant with part 11.

Two FDA guidances on the use of computerized systems that may be of interest to you include FDA's guidances for industry entitled "Part 11, Electronic Records; Electronic Signatures-Scope and Application" (http://www.fda.gov/oc/gcp/guidance.html) and the "Computerized Systems Used in Clinical Trials" (http://www.fda.gov/oc/gcp/draft.html , see posting dated 9/30/04). These guidances explain FDA's current thinking on practices that can help interested persons comply with the regulations. (As you probably know, regulations are legally binding while guidances are not. Information contained in guidances represent the agency's current thinking on a topic. The guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Interested persons can use alternative approaches if the approaches satisfy the requirements of the applicable statutes and regulations.)

The Part 11 Scope and Application guidance describes FDA's thinking on how firms can comply with part 11 requirements. As you will see when you read this guidance, if electronic records are used in lieu of paper records, those e-records and the systems that create those records must be part 11 compliant. As the guidance goes on to state, a decision to validate a computerized system, and the extent of validation, should take into account the impact the systems have on one's ability to meet "predicate rule" requirements". One should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. [In the case of clinical trials, predicate rules include those regulations that govern good clinical practice (e.g., 21 CFR 312 and 812).] FDA recommends that any decision on system validation be based on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity.

The guidance continues by addressing copies of records (see page 7). As this guidance notes, FDA recommends that persons supply copies of electronic records to FDA investigators by:

- producing copies of records held in common portable formats when records are maintained in these formats;
- using established automated conversion or export methods, where available, to make copies in a more common format (e.g., PDF, XML, SGML)

The copying process used must produce copies that preserve the content and meaning of the record. If one has the ability to search, sort, or trend part 11 e-records, copies given to FDA should provide that same capability if it is reasonable and technically feasible (e.g., print outs of the various data sorts used for trending/tracking study information).

Records must be retained in accordance with the requirements of the predicate rule (e.g., 21 CFR 312.57(c), 312.62(c); 21 CFR 812.140 and 145). Any decision on how to maintain records needs to be based on a justified and documented risk assessment and a determination of the value of the records over time. The guidance concludes by noting that FDA does not intend to object if one decides to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper; or to a standard electronic file format (e.g., PDF, XML, SGML). As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, one can delete the electronic version of the records. Additionally, paper and electronic record and signature components can co-exist as a hybrid system (see guidance for further information) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

Since computerized systems used for clinical trials contain critical study data, activities related to the conduct of clinical trials can be considered "high risk" and every effort should be made to make certain the records are accurate, reliable, have integrity, are readily available, and are authentic. Guidance on controls that can be used for computerized systems used in clinical trials can be found in the FDA guidance with the same name. I strongly suggest you review that guidance as it addresses the use of computers (hardware, software, firmware) in the clinical test environment.

I hope this information is helpful to you.

Sincerely,

Patricia M. Beers Block
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-----Original Message-----
From: [redacted]
Sent: Monday, December 05, 2005 4:36 PM
To: gcpquestions@oc.fda.gov
Subject: Source Documents in Clinical Studies

Ladies and Gentlemen:

[redacted] on a clinical study. The sponsor has mandated that the study be "paperless". Instead of capturing our initial observations, history, etc. on paper, the sponsor has told us we must put it into a computer. The computer, at the end of the study will then generate "source documents" and CRF's from the data we have entered. There will be nothing in our files to demonstrate what we observed at the patient visits since we are entering this information simultaneously with the patient visit. We cannot print out the information we have placed into the computer. I am concerned that this procedure would not allow us to be able to reconstruct the trial, if necessary, as if required by 1.51of the

GCP guidelines. In fact in one situation, the data we had entered was lost and we were required to reconstruct. We had, however, paper source for that particular visit and was able to provide the sponsor with the reconstructed data. Could you please give us some guidance on whether this "paperless" source study would pass an FDA inspection? We have kept paper source up to this point, however, the sponsor in insisting we stop with paper source and do everything on the computer. I do not want to do anything that could hurt us in the future if there is an audit of our facility. Thank you for your time.

[redacted]