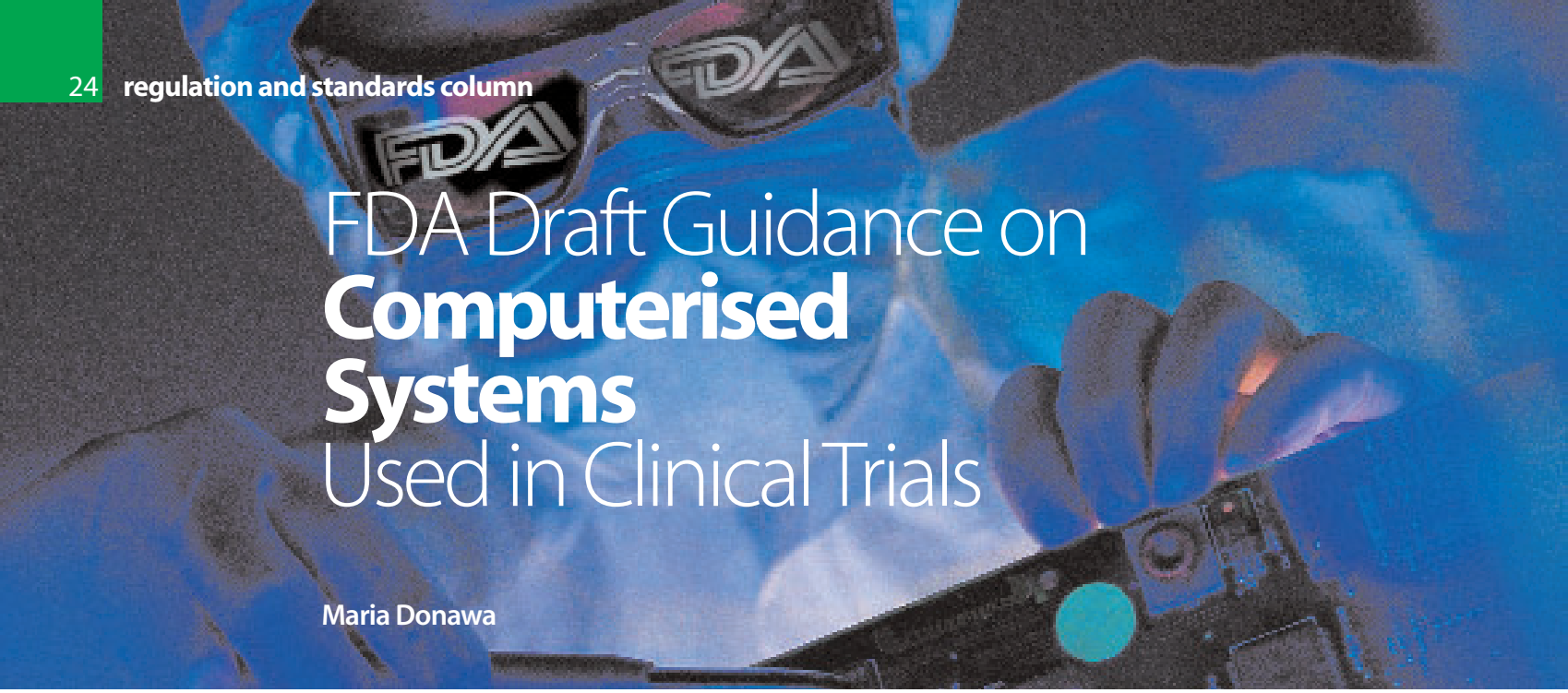

FDA Draft Guidance on **Computerised Systems** Used in Clinical Trials

Maria Donawa

When using computer systems to manage clinical studies, it is important to understand how these systems should be controlled and, for studies intended to support United States (US) regulatory submissions, when and how US regulations on electronic records and signatures apply. This article discusses these issues and a draft guidance document.

When US regulations apply

Sponsors of medical device clinical studies need to be clear about when United States (US) regulations apply to their studies and when they do not. If a clinical investigation is conducted outside the US under the US Investigational Device Exemption (IDE) regulation, Title 21 Code of Federal Regulations (CFR) Part 812, the investigation is subject to US regulations regarding the conduct of clinical investigations and the control of electronic records and signatures. If a clinical investigation is conducted outside the US and not under an IDE, it is not subject to US regulations. However, the sponsor of a clinical investigation conducted in this manner may wish to submit the results of the investigation to Food and Drug Administration (FDA) in support of a US regulatory submission for device clearance or approval. In recent years, acceptance by FDA of clinical investigations conducted outside the US and not under an IDE has increased, but this acceptance is based on the judgement that the clinical data submitted to the agency are valid. To be more certain of FDA acceptance, sponsors should take US regulations concerning the conduct of clinical investigations into consideration when clinical investigations are conducted outside the US and not conducted under an IDE. They should also consider following the recommendations made in relevant guidance documents, including the guidance document on computerised systems used in clinical trials, which is discussed below.

Need for updated guidance

In September 2004, FDA published a draft guidance document on computerised systems used in clinical trials,[1] which is consistent with the new FDA policy on the electronic records and signature regulation (21 CFR Part 11). When final, it will replace the current guidance document on the same subject.[2] Interested parties were invited to submit written or electronic comments on the draft recommendations by 3 January 2005. The comments received will be taken into consideration in formulating the final guidance document. Therefore, the final guidance document when published may differ somewhat from the draft document.

Wide applicability

The guidance document provides advice on meeting FDA expectations on clinical data quality when computer

Dr Maria E. Donawa

physician, pathologist and pharmacist with 25 years' regulatory experience, worked with the US FDA before becoming President of Donawa & Associates Ltd, an international consultancy firm, which provides clinical research, quality management system, regulatory affairs, and European Authorised Representative services to medical technology companies.

systems are used to create, modify, maintain, archive, retrieve or transmit clinical data. As such, the guidance document has a potentially wide applicability. That is to say, FDA states that the primary focus of the guidance is on computerised systems used at clinical sites to collect data, but that the principles set forth may also be appropriate for computerised systems belonging to contract research organisations, data-management centres and sponsors. FDA also states that the principles in the guidance document may be applied where supporting data or source documents are created

- in hard copy and later entered into a computerised system
- by direct entry by a human into a computerised system
- automatically by a computerised system.

General principles

The guidance document includes a list of general principles and recommendations, which reflect current FDA enforcement policies. Because these recommendations are based on common sense and will help ensure the quality and integrity of clinical data, all parties involved in using computer systems in clinical studies should review these recommendations and follow those they consider appropriate and applicable to their studies.

For example, FDA recommends that study records include the identification of the software and hardware used to create, modify, maintain, archive, retrieve or transmit data. Following this recommendation will facilitate the investigations of certain types of problems or questions, which may occur regarding data collection and quality.

FDA also recommends that computerised systems are designed so that all requirements assigned to these systems in a study protocol are satisfied such as the need to record data in metric units and to preclude errors in data creation, modification, maintenance, archiving, retrieval or transmission.

Another recommendation concerns the need for audit trails. FDA states that an audit trail that is electronic or consists of other physical, logical or procedural security measures to ensure that only authorised additions, deletions or alterations of information in the electronic record have occurred may be needed. Companies are advised to conduct a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information may be compromised, and system vulnerabilities.

Specific recommendations

In addition to providing general principles, the guidance document provides recommendations on specific activities related to the control and management of computer systems used in clinical trials, including those related to standard operating procedures (SOPs), data entry, system features, system security, system dependability, system controls, training of personnel, copies of records and record inspection, and certification of electronic signatures.

For example, FDA recommends that SOPs be developed for

- system setup and installation
- data collection and handling
- system maintenance, data backup, recovery and contingency plans
- security
- change control
- alternative recording methods in the case of system unavailability.

The recommendations concerning data entry include computer-access controls, audit trails or other security measures, and date/time stamps. For example, readers should note that FDA has stated repeatedly that it intends to enforce certain controls for closed systems such as those specified by section 11.10(d) of 21 CFR Part 11, which require procedures for limiting system access to authorised individuals. Closed systems are defined as an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system. Therefore, the guidance document states that clinical data entry systems must be designed to limit access so that only authorised individuals are able to input data. Examples of methods for controlling access are provided such as the use of combined identification codes. However, the document also recommends that each user of the system has an individual account into which the user logs in at the beginning of a data-entry session, inputs information (including changes) on the electronic record, and logs out on completion of the data-entry session. Additional recommendations concerning access to the system are also provided.

In the discussion of system features, FDA recommends that the manner in which records are maintained is based on "predicate rule" requirements, risk assessment, and a determination of the value of the records over time. The term predicate rule refers to underlying requirements specified in US regulations such as the Federal Food, Drug, and Cosmetic Act, other than 21 CFR Part 11.

Regarding system security, FDA recommends that SOPs be developed and implemented for handling and storing the system to prevent unauthorised access. In addition, FDA recommends that controls be implemented to prevent, detect and mitigate effects of computer viruses, worms or other potentially harmful software code on study data and software. The importance of this recommendation cannot be over emphasised in view of the prevalence of these potential sources of problems and attacks.

In the section on system dependability, the guidance document states that FDA intends to exercise enforcement discretion regarding all Part 11 requirements for legacy systems. These are systems that were fully operational prior to 20 August 1997, which is the effective date of Part 11. However, all the following criteria must be met for a specific system.

- The system was in operation before the Part 11 effective →

→ date.

- The system met all applicable predicate rule requirements prior to the Part 11 effective date.
- The system currently meets all applicable predicate rule requirements.
- There is documented evidence and justification that the system is fit for its intended use.

Useful information

As stated previously, the final guidance document may contain some changes made in response to comments submitted to FDA on the draft guidance document. In spite of this possibility, the draft document contains useful information on the precautions that should be taken when computer systems are involved in the conduct of clinical investigations. Therefore, readers are advised to review the draft document, follow recommendations that they deem to be useful in ensuring the validity of their clinical data, obtain the final document when it is issued, and make any adjustments necessary based on any modifications made to the guidance document.

References

1. US FDA Guidance for Industry, "Computerised Systems Used in Clinical Trials," September 2004, downloadable from www.fda.gov/cder/guidance/6032dft.pdf
2. US FDA Guidance for Industry, "Computerised Systems Used in Clinical Trials," April 1999, downloadable from www.fda.gov/ora/compliance_ref/bimo/ffinalcct.pdf mdt

Maria E. Donawa
Donawa & Associates Ltd,
Piazza Albania 10, I-00153 Rome, Italy,
tel. +39 06 578 2665, fax +39 06 574 3786
e-mail: medonawa@donawa.com www.donawa.com