FDA Considerations

Related to Maintaining Clinical Trial Records in Electronic Form

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I. Introduction

For more than a decade, the Food and Drug Administration (FDA) has recognized the expanded use of computerized systems by the various industries that the agency regulates. Electronic records and related automation efforts extend to manufacturing process controls, materials resources controls, laboratory information systems, clinical trial information systems, and electronic data interchange activities. FDA’s recognition of the increasing use of computerized systems is reflected in regulations and guidance issued by the agency over the past several years, encouraging the use of the new technologies.

FDA’s guidance concerning the use of computerized systems for clinical trials provides information on quality standards for the creation, modification, and transmission of clinical trial data intended for submission to FDA. While most institutions recognize the regulatory requirements involved in conducting clinical studies, many health professionals are unfamiliar with the regulations and agency guidance governing the use of computer systems in those studies. As the industry moves increasingly toward electronic-based recordkeeping, it will become progressively more important for all sectors of the healthcare industry to understand the regulatory considerations pertaining to the establishment and maintenance of electronic clinical trial records.

II. Importance of FDA Clinical Trial Records

Clinical trial recordkeeping requirements are intended to serve as another layer of protection for the human participants in clinical research of FDA-regulated products. All clinical investigations regulated by FDA—be they in support of applications for research or marketing permits for drugs, biologics, or medical devices—must meet certain requirements and standards of conduct, including the protection of the rights and safety of human subjects involved in the investigations.

FDA regulations requiring comprehensive clinical trial records to protect the rights and safety of patients, including the investigational device exemptions, institutional review board, and informed consent regulations, also are intended to ensure the integrity of research data and assist in the development of concise, accurate infor-
information for marketing application submissions. Clinical trial record requirements enable the agency’s review of marketing applications to proceed more quickly and efficiently, thus benefiting the consumer by facilitating the prompt availability of safe and effective drugs and devices.6

A. Records Requirements Generally

Section 505(i) of the Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes FDA to promulgate regulations providing an exemption from statutory requirements for qualified experts to investigate the safety and effectiveness of drugs.7 Section 520(g) of the FFDCA provides the authority for FDA to develop regulations regarding the investigational use of medical devices.8 Both statutory provisions explicitly require the establishment and maintenance of records and reports sufficient to ensure compliance with procedures and conditions developed by the agency to protect the public health and safety.9

In 1962, FDA initially proposed regulations on new drugs for investigational use, including a requirement that study investigators maintain records.10 The legislative history of § 505(i) of the FFDCA, part of the Drug Amendments of 1962,11 demonstrates Congress’ understanding of the importance of clinical trial records:

[I]nvestigators are required to maintain records on the investigation. The Department has proposed strengthening regulations to provide greater safeguards in investigational drug use. The bill approves strengthening regulations and provides that the regulations may require, among other things, * * * the establishment and maintenance of adequate records * * * to facilitate the evaluation of the safety and effectiveness of the new drug, when an application is filed * * *. [This section also] amends the prohibited acts section of existing law, section 301(e), to forbid the failure to establish or maintain any required record, either on an investigational use of drugs or on clinical experience.12

The congressional intent demonstrated here, coupled with the ample authority set forth in sections 505 and 520 of the FFDCA, provide the basis for the regulatory scheme of clinical trial record requirements for drugs, medical devices, and biologics.

Pursuant to the FFDCA, FDA promulgated rules establishing the agency’s authority to inspect all records relating to clinical investigations conducted under the regulations governing investigational new human and animal drugs and investigational devices,13 regardless of how those records are created or maintained.14 FDA established its Bioresearch Monitoring (BIMO) Program, a comprehensive system of on-site inspections and data audits, to monitor the conduct and reporting of clinical trials.15 The BIMO program is intended to ensure that supporting data from clinical trials conform to FDA regulations and meet the highest standards of quality and integrity.16

To ensure the quality and integrity of data submitted to the agency in support of new product approvals and to protect the rights and welfare of human subjects involved in clinical trials, FDA must be able to verify the quality and integrity of the data during FDA on-site inspections and audits. For purposes of accurate regulatory decision-making, clinical trial data must meet certain fundamental elements of quality whether they are collected or recorded electronically or on paper.17 Accordingly, clinical data offered in support of new and investigational products must be attributable, legible, contemporaneous, original,18 and accurate.

B. Recordkeeping and Investigational New Drugs

The FFDCA authorizes FDA to promulgate regulations to govern the use of experimental drugs.19 Drug manufacturers that wish to study such a drug must apply for an exemption from the otherwise applicable premarketing approval requirements of the FFDCA20 by submitting an investigational new drug application (IND). An IND allows qualified experts or investigators to conduct investigations on the safety and effectiveness of the experimental drug on behalf of the IND sponsor.21

The IND regulations set forth numerous requirements intended to safeguard the health of subjects in clinical trials and ensure the safety and efficacy of the investigational drugs. Before initiating a clinical study, an IND sponsor must provide FDA with extensive information concerning the proposed study, including a detailed investigational plan, known as the study protocol, to which all investigators must adhere.22

FDA published the current IND regulations in 1987.23 The final rule imposed explicit recordkeeping requirements on clinical study investigators, including: maintenance of adequate records concerning the disposition of drugs subject to the IND;24 preparation and maintenance of accurate patient case histories;25 two-year retention of required records;26 provision of progress, safety, and final reports to the IND sponsor;27 and access by FDA to required records.28

The IND final rule characterized the requirements as important to “help sponsors of clinical investigations prepare and submit high quality . . . applications and permit FDA to review them efficiently and with minimal delay.”29
Thus, compliance with IND regulations, among other things, has two effects: pharmaceutical manufacturers are able to take their clinical trial information and use it to prepare marketing applications to FDA; and FDA is able to ascertain the integrity and accuracy of those submissions.

C. Recordkeeping and Investigational Device Exemptions

As with investigational drugs, there are exemptions for medical device manufacturers that want to use investigational devices in clinical studies to collect safety and effectiveness data in support of premarketing submissions to FDA. First and foremost, a sponsor generally must receive approval of an investigational device exemption (IDE) application from FDA. An approved IDE permits the lawful shipment of a device for the purpose of conducting investigations without requiring that the investigational device comply with other requirements of the FFDCA that would apply to devices in commercial distribution.

Before the study begins, among other duties, the sponsor of the clinical trial also is responsible for: selecting qualified study investigators and providing them with the information they need to conduct the investigation properly; ensuring proper monitoring of the investigation; and obtaining review and approval from an Institutional Review Board (IRB). While they also have other responsibilities, the investigators must obtain informed consent from all study participants; ensure that the investigation is being conducted according to the signed agreement, the study protocol, and applicable FDA regulations; control the device(s) under investigation; and prepare and maintain all records, reports, and related information required by FDA regulations.

III. FDA’s Electronic Record Regulations, 21 C.F.R. Part 11

The development of regulations addressing electronic records and signatures was prompted by the regulated industry’s desire to obtain input from FDA on the use of paperless manufacturing record and signature systems under existing current good manufacturing practice (CGMP) regulations. In the early 1990s, there was an increased interest in electronic systems, but there were no regulatory provisions sanctioning the maintenance or submission of required records in electronic format. Over several years, FDA consulted with various stakeholders in developing rules that addressed the accuracy, reliability, and validity of electronic records. Those regulations, otherwise known as 21 C.F.R. Part 11, were finalized in March 1997, with the stated intent of permitting the widest possible use of electronic technology while supporting FDA’s mission to protect the public health.

Part 11, which applies to all FDA program areas, pertains to any electronic records that are created, modified, maintained, archived, retrieved, or transmitted pursuant to any FDA records requirement. Part 11 also applies to electronic records submitted to FDA under the FFDCA or the Public Health Service Act, even if not specifically identified in agency regulations. Pursuant to the regulations, all computer systems (including hardware and software) and related documentation maintained under Part 11 are subject to—and must be made available for—FDA inspection.

Part 11 provides criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. Where paper records are required by an existing regulation or “predicate rule,” Part 11 provides the option of maintaining those records in paper or electronic form. Part 11 sets forth the criteria for ensuring the integrity and authenticity of electronic records, as well as for documenting and validating authorized change processes to systems and software involved in the creation and maintenance of
such records. While maintenance and submission of records in electronic format are not required, once a regulated entity chooses to keep any required records in electronic format or submit such records electronically to FDA, it must comply with the provisions of Part 11.

After Part 11 became effective in August 1997, there was a flurry of activity and discussion concerning the interpretation and implementation of the regulations. Among industry, contractors, and the agency itself, there were concerns that the scope of the regulations had expanded beyond FDA’s stated intent. The agency documents interpreting Part 11 were seen as: discouraging innovation and technological advances; significantly increasing the cost of compliance; and putting unnecessary restrictions on the use of electronic technology in a manner inconsistent with FDA’s originally stated intent. FDA participated in discussions with industry and issued several new guidance documents and a Compliance Policy Guide (CPG) to clarify its approach. However, those efforts ultimately failed. In February 2003, the agency announced its intention to undertake a broad reexamination of Part 11, withdrawing the guidance documents and CPG as no longer representative of the agency’s regulatory approach.

In August 2003, as part of FDA’s CGMP initiative for human and animal drugs and biologics, the agency issued a final guidance document clarifying Part 11. According to the August 2003 guidance, the scope of Part 11 has been narrowed to the following categories of records:

- Records that must be maintained in electronic format in place of paper;
- Records that are relied upon to perform regulated activities, when maintained in electronic format in addition to paper format;
- Records submitted to FDA, pursuant to a predicate rule, in electronic format; and
- Electronic signatures that are intended to be the equivalent of handwritten signatures.

Excluded from the purview of Part 11 are records not required by predicate rules and records used only in generating submissions that are not otherwise required by predicate rules.

The guidance announced FDA’s plans to initiate rule-making re-examining Part 11 as part of the agency’s CGMP initiative for human and animal drugs and biologics. At that time, FDA may update and revise any unclear provisions of the regulation. In the interim, the agency will be exercising enforcement discretion as to the following Part 11 requirements:

- Validation of computer systems, 21 C.F.R. § 11.10(a);
- Computer-generated, time-stamped audit trails, 21 C.F.R. § 11.10 (e), (k)(2);
• Generating copies of records, 21 C.F.R. § 11.10 (b);
• Protection of records to enable their accurate and ready retrieval throughout the records retention period, § 11.10 (c); and
• All requirements for legacy systems (those systems that were operational before the effective date of Part 11 (August 20, 1997)).

FDA also will be exercising enforcement discretion regarding any corresponding requirements in 21 C.F.R. § 11.30, regarding controls for open systems. However, until such time as FDA addresses Part 11 through a new rulemaking, the agency still may take regulatory action for noncompliance with any underlying predicate rules. No new rulemaking is expected for at least two years.

IV. Guidance for Industry: Computerized Systems Used in Clinical Trials

When the various Part 11 guidance documents and related compliance policy guide were withdrawn in February 2003, FDA left in place the April 1999 guidance for industry entitled, “Computerized Systems Used in Clinical Trials.” For a time, it offered the most complete guidance for any regulated sector on the practical application of Part 11 to required records and documentation for the clinical trials community.

The Computerized Systems guidance deals with the basis for consideration of computer system records as “source data/source documents.” It also provides guidance on the nature and extent of required computer system validation. Because of the importance of clinical trial data in demonstrating the safety and efficacy of regulated products, it is crucial that data from computerized systems are recognized as no less reliable than data in paper form.

The clinical trial data submitted to FDA form the basis for the agency’s determination of safety and efficacy of new human and animal drugs, biologics, and medical devices. Thus, clinical trial data have broad public health significance and must be of the highest quality and integrity. As previously stated, part of FDA’s intent in promulgating Part 11 was to ensure the reliability of electronic information. The Computerized Systems guidance document was designed to ensure that Part 11 is applied to these records in such a way as to give FDA and the study sponsors confidence in the integrity of the data used to support claims of product safety and efficacy. In order to rely upon clinical trial data in the product approval process, FDA must be able to verify the quality and integrity of the data during its on-site inspections.

FDA outlined its policy on the use of electronic records in clinical trials because the agency has a particular interest in maintaining the integrity of those records. In addition to the previously discussed public health mission, FDA also is concerned about the potential for fraudulent data collection or record modification. By placing strict controls on electronic records, the agency ostensibly is precluding any intentional manipulation of clinical trial records for fraudulent purposes.

While Part 11 defines the requirements for capture, storage, retrieval, maintenance, and security of data, the Computerized Systems guidance document spells out the utilization of Part 11 records for compliance with FDA data quality standards for clinical trials. The guidance expands upon the regulations by defining the standard operating procedures (SOPs) necessary for compliance. The guidance document recommends that SOPs be created, at a minimum:

• System set-up and installation;
• Data collection and handling;
• System maintenance;
• Data back-up, recovery, and contingency plans;
• Security; and
• Change controls.

To elucidate the recommended SOPs, the guidance discusses data entry requirements, such as audit trails and electronic signatures, and date/time stamps; recommended system features, particularly those that allow for the collection of quality data as well as ease of data retrieval and study reconstruction; software validation, to determine system dependability; system controls, including contingency plans and back-up and recovery of electronic data; training of personnel and documentation of that training; and FDA records inspection requirements.

The guidance explains that the computerized systems should be designed to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission. Study sponsors also should ensure that any computerized system used in conjunction with a clinical trial satisfies all of the requirements set forth in the study protocol. Persons using the data from computerized systems should have confidence that the data are no less reliable than data in paper form. There are certain fundamental elements of quality that must be present for both paper and electronic records. Data submitted in support of a marketing application must be attributable, original, accurate, contemporaneous, and legible.
The Computerized Systems guidance document is intended to be applied where source documents are created (1) in hard copy and later entered into a computerized system; (2) by direct entry by study personnel into a computerized system; and (3) automatically by a computerized system. Source documents should be retained to enable a reconstruction and evaluation of a clinical trial, and clinical investigators are advised to retain either the original or a certified copy of all source documents sent to any sponsor or contract research organization, including query resolution correspondence.

The guidance focuses primarily on computerized systems used to collect data in clinical trials. However, the same principles may be applied to computerized systems maintained by contract research organizations, data management centers, and sponsors. The guidance does not address electronic submissions or their transmission to the FDA.

FDA recently released an updated draft guidance for industry. The draft guidance, also entitled “Computerized Systems Used in Clinical Trials,” was revised to be consistent with FDA policy as reflected in the August 2003 guidance for industry on the scope and application of Part 11. The new guidance also is consistent with FDA’s efforts to harmonize its policy with international standards for clinical trials.

The draft guidance adds to the list of SOPs recommended by the April 1999 guidance. In addition to the six previously stated areas, FDA recommends SOPs outlining alternate methods for recording data in the event of a system failure. The “General Principles” contained in the April 1999 guidance also are substantially modified. The draft guidance provides the following new recommendations:

- Original source documents or certified copies should be retained at the site where the investigation was conducted to assist in meeting regulatory requirements (and in the reconstruction and evaluation of the trial);
- Pursuant to the relevant regulations, records relating to INDs must be adequate and accurate; records relating to new animal drugs for investigational use must be complete; and IDE records must be accurate, complete, and current;
- An audit trail may be needed to facilitate compliance with applicable records regulations. 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;
- Data should be retrievable in a manner that ensures that information regarding each individual subject in a study is attributable to that subject; and
- Security measures should be put into place to prevent unauthorized access to data.

The draft guidance has not yet been finalized; FDA will be accepting comments on the draft recommendations until January 2005. Once the draft guidance is finalized, it will supersede the April 1999 version.

V. The Use of Computerized Systems in Records Management for Clinical Trials

For the past twenty years, there has been an expectation that the advent of computers would lead to an associated increase in the use of electronic data capture (EDC) and related technologies. However, despite the widespread use of computer systems in other sectors of the healthcare industry and the fact that industry was the impetus behind the development of FDA standards for electronic records, the reality is that the transition to such records in clinical trials has only recently begun to hit its stride.

Leading up to 2000, concerns about reliability and systems standards, coupled with industry uncertainty regarding FDA’s regulatory approach to electronic records, resulted in a slow transition to EDC for clinical trials. Part of the delay in implementing EDC has been the price of converting study data to electronic format. The annual cost of converting clinical trial data to computerized systems has been estimated at over $122 million. However, advances in technology have increased the usability and reliability of computerized systems, and the increased
CDISC is developing models and standards to support various types of electronic data interchanges within the clinical trial process. These include:

- **Operational Data Model (ODM):** a format for interchange and archive of data collected from various sources in clinical trials;
- **Submission Data Standards (SDS):** intended to guide the organization and format of standard clinical trial data submitted to federal agencies such as FDA;
- **Laboratory Data Model (LDM):** a standard model for the acquisition and interchange of clinical trial laboratory data; and
- **Analysis of Dataset Model (ADaM) (specifically for statistical reviewers):** a set of guidelines for analysis of data used to generate statistical results for submission to an agency such as FDA.

The data models are being developed by committees that work together to propose models for review and refinement. FDA is particularly interested in the work of the SDS and ADaM groups as it pertains to agency submissions; the agency already has participated in a pilot test of electronic data submission pursuant to the SDS model.

In an effort to improve its efficiency in processing, archiving, and reviewing industry submissions of marketing applications (NDAs, ANDAs, BLAs), INDs, and related submissions (master files, advertising, and promotional labeling) in electronic format, FDA also made available the CDISC information as part of its August 2003 guidance to industry entitled “Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions.” The guidance is based on the Electronic Common Technical Document specifications developed by the International Conference on Harmonization, consistent with FDA’s good guidance practices regulation.

While compliance with any existing FDA recordkeeping regulation through the use of electronic records currently is optional, Part 11 is only the first step in what likely will be the eventual mandatory electronic submission of clinical trial records. With the use of computerized systems for some facets of clinical studies becoming more routine, it is to be expected that electronic records eventually will become the norm. Again, it is important to keep in mind that once a regulated entity chooses to keep any required records in electronic format or submit such records electronically to FDA, it must comply with the provisions of Part 11.

**VI. Conclusion**

As electronic records become more prevalent in clinical trial records management, it is imperative that those institutions and personnel involved become familiar with regulatory considerations pertaining to the use of those records. While FDA’s ultimate interpretation of Part 11 may still be in flux for other areas in which records are required, it would benefit the clinical trials community to learn and implement the existing guidance on the use of computerized systems in the creation, modification, and transmission of clinical trial data for submission to FDA. Understanding, creating, and securing compliant systems now will ease the eventual transition to a system of electronic submissions.

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2 See, e.g., 21 C.F.R. § 50.1.

3 See 21 C.F.R. Part 812.

4 See 21 C.F.R. Part 56.

5 See 21 C.F.R. Part 50.

6 See Food and Drug Administration, New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8798, 8799 (Mar. 19, 1987) (discussing the need for updated regulations to ensure FDA’s ability to monitor the safety of patients).


9 21 U.S.C. §§ 355(i)(1)(c); 360(j)(2)(B)(ii). Additional sections of the FFDCA provide for premarket applications to be filed with FDA, but they are beyond the scope of this article. They include FFDCA §§ 403 (foods); 409 (food additives); 412 (infant formulas); 413 (new dietary ingredients); and 721 (color additives).


13 See generally 21 C.F.R. Parts 312, 511, 812 (setting forth standards for investigational new drugs, investigational new animal drugs, and investigational device exemptions, respectively).

14 See, e.g., 21 C.F.R. §§ 312.58, 312.68, and 812.145 (discussing the scope of inspection and records availability).


16 Id.


18 Even prior to the advent of computerized systems, FDA’s regulations allowed for the use of certified copies in place of original documents provided the copies are identical and have been verified as such. See Food and Drug Administration, Compliance Policy Guide 130.400 (7150.13) (May 1979), available at www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-400.html.


21 The “sponsor” of a drug study is generally the pharmaceutical company filing the IND.

22 21 C.F.R. § 312.23(a)(6). The protocol must include a statement of the objectives and purpose of the study; information on the clinical investigators; a description of the study; information on the criteria of participant selection; dosing information; observations and measurements to be made; and a description of the clinical procedures, laboratory tests, and/or other measures to be used to monitor the effects of the drug and minimize risk in study participants.


24 21 C.F.R. § 312.62(a).

25 21 C.F.R. § 312.62(b).

26 21 C.F.R. § 312.62(c).

27 21 C.F.R. § 312.64.

28 21 C.F.R. § 312.68.

The guidance explains, “FDA may inspect all records that are intended to support submissions to the Agency, regardless of how they were created or maintained.” Computerized Systems Used in Clinical Trials at 2.


65 CenterWatch, Clinical Trials Advisor (Nov. 7, 2002), at 5.


67 See CenterWatch, Clinical Trials Advisor, November 7, 2002, at 5.


71 See id.

72 Data Change is Costly, CDISC Says, Clinical Trials Advisor (Nov. 7, 2002), at 5.


74 See id.

75 See FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data, available at www.fda.gov/cder/regulatory/ersr/ectd.htm


77 See 21 C.F.R. §§ 812.57, 312.62.

78 See 21 C.F.R. § 511.1(b)(7)(ii).

79 See 21 C.F.R. §§ 812.140(a), (b).


83 See id.

84 Data Change is Costly, CDISC Says, Clinical Trials Advisor (Nov. 7, 2002), at 5.


92 CenterWatch/CDISC Survey, November 2002.

93 See FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data, available at www.fda.gov/cder/regulatory/ersr/ectd.htm


95 See 21 C.F.R. §§ 812.57, 312.62.

96 See 21 C.F.R. § 511.1(b)(7)(ii).

97 See 21 C.F.R. §§ 812.140(a), (b).


101 See id.

102 Data Change is Costly, CDISC Says, Clinical Trials Advisor (Nov. 7, 2002), at 5.


111 Industry Consortium Works to Advance Data Standards, Clinical Trials Advisor, November 7, 2002, at 5.


113 The International Conference on Harmonisation and its multi-disciplinary working group were established to facilitate international electronic communication by evaluating and recommending “Electronic Standards for the Transfer of Regulatory Information” in an effort to meet the requirements of pharmaceutical companies and regulatory authorities worldwide. See generally www.fda.gov/cder/m2/backgrnd.htm.

114 See 21 C.F.R. § 812.100.