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Dissecting Electronic Signatures for the Life Sciences

By Robert Finamore and John Harris

Electronic signatures (e-signatures) can save substantial time and money. As a result, according to Forrester Research, the use of e-signatures has grown at an average annual rate of 53% since 2012, and more than 700 million documents and transactions are expected to be signed electronically by 2017.

This trend applies to clinical research and other life science activities. For example, a nationally renowned clinical research institute that implemented an e-signature pilot program reduced the time required to obtain signatures on clinical trial documents from a range of 19 to 58 days to only three to four days.

The FDA's definition of e-signatures is found in 21 CFR Part 11: Electronic Records, Electronic Signatures. These regulations specify FDA's requirements for using records and signatures in electronic form to meet the agency's recordkeeping requirements. However, the title of the regulation itself uses the term "electronic signature," which can be misconstrued. The regulation deals with several different types of signatures in electronic form. The different types of signatures include "standard" electronic signatures, digital signatures, and handwritten signatures captured electronically. Before adopting an e-signature technology, it is important to understand the substantial differences between them.

Electronic Signatures

Most people think of "standard" e-signatures when considering Part 11. FDA defines an e-signature as "a computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature." (§11.3(b)(7)) This definition indicates that some information must be entered electronically and associated to a record (or document) for that record to be considered signed. Information about the signature is displayed with the record to indicate that it has been signed. (§11.50) By FDA's definition, there are two types of standard e-signatures — biometric and non-biometric:

Biometric Signatures

As defined in Part 11, biometric e-signatures involve "a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s), where those features and/or actions are both unique to that individual and measurable." (§11.3(b)(3)) This unique measurement must be captured every time a record is signed, and it must be securely linked to the signed record.

Examples of biometric signatures include fingerprint and iris scans. These scanning technologies have to find a balance between resolution that is too low to prevent false positives (which would allow for fraudulent signing) and too high to prevent false negatives (which would create operational efficiencies). Another downside of this type of signature is that it normally requires attaching measurement hardware to a computer for execution of the signature. As a result, biometric signatures are not commonly used in the life sciences.

Biometric signatures must comply with both the General Signature Requirements and Electronic Signature Requirements, as defined in §11.50, §11.70, §11.100 and §11.200(b) of the Part 11 regulation.

Non-Biometric Signatures

The other type of standard e-signature is the non-biometric signature. This type of signature requires entry of two or more distinct signature components into the computerized system as the e-signature execution action. A user ID and password might constitute these distinct components, although there could be additional or alternate components, such as a badge scan instead of a user ID, or the additional entry of a code from a token or other code-generating device.

Because most modern computerized systems already incorporate logical security functionality (e.g., user names and passwords), non-biometric signatures are the most common type of e-signature implemented in FDA-regulated applications, even though the regulations require additional controls for this type of e-signature. (§11.300)

Non-biometric electronic signatures must comply with both the General Signature Requirements and Electronic Signature Requirements, as defined in §11.50, §11.70, §11.100, §11.200(a), and §11.300 of the Part 11 regulation.

Digital Signatures

Many e-signature applications in the life sciences might require a higher level of security than that provided by standard e-signatures. Digital signatures are a form of non-biometric electronic signatures and, and as defined by FDA, are based on "cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified." (§11.3(b)(5)) Digital signatures are typically implemented using Public Key Infrastructure (PKI), which involves obtaining and utilizing public and private keys that are provided and managed by a trusted third party. A digital signature becomes invalid if the document changes in any way. It is the only type of electronic signature that can provide true non-repudiation.

In addition to the applicable e-signature requirements mentioned above, digital signatures can also be used to fulfill the requirements for "open systems," as detailed in §11.30 of the Part 11 regulation.

For these reasons, organizations like SAFE-BioPharma, the European Medicines Agency, and the U.S. Drug Enforcement Agency (for prescriptions for controlled substances) require e-signatures to be digital signatures.

Digital signatures integrate signature verification into the document itself. Because the digital signature's cryptographic information is embedded directly into the electronic document, the signature proves its own integrity independently, meaning signers do not have to rely on a web link to the e-signature vendor to verify the signature's validity. Digital signatures also provide increased transparency of a signature's validity and the signing process, perpetual assurance of validity, and reduced risk from cyber threats.

Electronically Captured Handwritten Signatures

Another type of signature is the electronically captured handwritten signature. The FDA considers a signature handwritten if "the act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark." (§11.3(b)(8)) A common example of this method is the capture of the signature image via signing with a stylus on a digitizing pad or touch screen.

A common life sciences application for this type of signature is in sales force automation systems utilized by pharmaceutical sales reps in the field to capture the signatures of health care practitioners receiving drug samples. Such an electronically captured handwritten

signature is not considered a true electronic signature by FDA definition. It thus need not comply with the e-signature-specific requirements defined in §11.100-§11.300 of the Part 11 regulation. However, as a handwritten signature "executed to an electronic record," it does need to comply with the general signature requirements defined in §11.50 and §11.70 of the Part 11 regulation.

True electronic signatures can allow signers to use their finger, mouse or stylus to draw their signature, provided the required security controls for standard e-signatures are implemented.

Hybrid Systems

Even though they are not electronically captured, traditional handwritten "wet ink" signatures can also fall within the scope of Part 11. This circumstance can occur in a "hybrid system" that incorporates both hard copy and electronic record elements. An example of this method would be printing a copy of an electronic record and signing the paper, with the intent that the signature approves the electronic version of the record.

Although this type of signature application is relatively rare, it may be used in cases where the computerized system cannot support compliant e-signatures. Hybrid systems were not well considered when the Part 11 regulation was drafted; however, these hybrid signatures would fall within the definition of "handwritten signatures executed to electronic records" and would need to comply with §11.50 and §11.70 of the Part 11 regulation. The most common way to ensure a secure record/signature linkage is to record unique information (e.g., a checksum or hash) about the electronic record on the paper, so that if the record changes, the signature will be invalidated.

Compliance with Part 11 electronic signature requirements is required only for approvals and signings that are specifically required within FDA predicate regulations, i.e., those that require companies to approve and maintain certain records or submit signed records to the agency as part of compliance. Within clinical research, records with signature requirements include institutional review board (IRB) documentation, study protocols, informed consent records, and certain principal investigator statements and agreements, among others. There are also signature requirements for key submission documents, such as INDs, NDAs and IDEs. Table 1 presents many, but not all, signature requirements from clinical research regulations. When electronic signatures are used to fulfill these requirements, Part 11 compliance is necessary.

Table 1. Clinical Research Signature Requirements

CFR Section	Signature Requirement
50.23(d)(1)(v), 50.24(a), 56.102(g), 56.102(m), 56.103(a), 56.109(a), 312.30(a)(2), 812.2(b)(1)(ii), 812.42, 812.62(a)	IRB approval of a clinical investigation, including approval of the investigational new drug protocol and the administration of the investigational new drug
50.23(d)(3)	IRB approval of (i) the required information sheet, (ii) the adequacy of the plan to disseminate information on the investigational product, (iii) the adequacy of the information and plans for its dissemination to health care providers, and (iv) an informed consent form

CFR Section	Signature Requirement
50.24(a)(6), 50.27(a), 56.115(a)(1)	IRB approval of informed consent procedures and an informed consent document; IRB approval of procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation
50.27, 812.140(a)(3)	Written consent form signed and dated by the subject or the subject's legally authorized representative at the time of consent
50.27(b)(2)	IRB approval of a written summary of what is to be said to the subject or the representative (for a short form consent), and subject's or representative's signature on that short form, along with signatures of a witness and the person obtaining the consent
54.4(a)(1)	Form FDA 3454 (attesting to the absence of financial interests and arrangements) signed and dated and by the CFO or other responsible corporate official or representative
56.108(a)(4), 56.109(a), 312.30(b)(2)(i)(b), 312.66, 812.35(a)(1), 812.35(b), 812.62(a)	IRB approval of changes in approved research, including updates to study protocol
312.23(a)(1)(ix)	Signature of the sponsor or the sponsor's authorized representative on IND cover sheet
312.23(b), 314.50(g)(1)	A reference to information submitted to the agency by a person other than the sponsor or applicant, which is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information
312.53(c)(1)	Form FDA-1572 signed by investigator
312.120(a)(i)	IEC approval before initiating a study, continuing IEC review of the ongoing study, and documenting the freely given informed consent of the subjects
312.120(b)(11)	Any signed written commitments by investigators maintained by the sponsor or applicant and made available for agency review upon request
314.50(a)(5), 314.94(a)(1), 814.20(a), 814.104(a)	Application signed by the applicant, or the applicant's attorney, agent or other authorized official
314.50(g)(3)	Written statement signed by the [non-applicant] owner of data that the applicant may rely on the data in support of the approval of its application
314.53(c)(2)(i)(Q)	A signed verification of compliance to 21 CFR 314.53
314.53(c)(4)	Declarations required by this section, signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official
314.72(a)(2)	Application form signed by the new owner
314.91(c)(2)	The request for a reduction in the discontinuance notification period signed by the applicant or the applicant's attorney, agent (representative), or other authorized official
314.200(d)(3)IV	A statement signed by the person responsible for such submission that it includes in full all studies and information specified in 314.200(d)
314.200(e)(2)IV	A statement signed by the person responsible for such submission, that all appropriate records have been searched and, to the best of that person's knowledge and belief, it includes a true and accurate presentation of the facts

CFR Section	Signature Requirement
601.2(a)	Application signed by the applicant or the applicant's attorney, agent or other authorized official
601.25(b)(3)VIII	If the submission is by a licensed manufacturer, a statement signed by the authorized official of the licensed manufacturer; if the submission is by an interested person other than a licensed manufacturer, a statement signed by the person responsible for such submission
812.20(a)(3)	A signed "Application for an Investigational Device Exemption" (IDE application)
812.20(b)(4)&(5), 812.36(c)(ix), 812.43(c), 812.100, 812.110(b), 812.140(b)(3)	Agreement signed by investigators
814.102	A completed, dated and signed request for HUD designation
814.124	IRB approval for administration of HUD
814.44(b)	Committee report and recommendation in the form of a meeting transcript signed by the chairperson of the committee

For all of the above-mentioned signature types, the signatures must be securely captured, stored and linked to their associated records. All these signatures can be legally binding and, as such, there must be a high degree of assurance that the signatures cannot be forged and cannot be repudiated by the signer. The type of signature that is best for a specific use in a specific organization depends on how and why the e-signatures are used, as well as how mission-critical or sensitive the records are to the organization, and the level of transparency, longevity, security and independence required. For example, using non-biometric e-signatures for IRB approvals in an electronic content management system is an efficient methodology. On the other hand, signing informed consent forms with non-biometric e-signatures at numerous research sites would be much more difficult. In the latter case, electronically captured handwritten signatures would likely make more sense, e.g., scanning a signed hardcopy or capturing the signature electronically on a tablet using a stylus.

Authors

Robert J. Finamore is Director, IT Compliance & Validation at QPharma, Inc., a regulatory compliance consulting firm based in Morristown, NJ. Contact him at 1.973.656.0011 or Robert.Finamore@qpharmacorp.com.

John Harris is Senior Vice President of Product Management at SIGNiX, an electronic signature solutions provider. Contact him at 1.877.890.5350 or jharris@signix.com.

