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In the next issue of
EDC Today:

SAS and ECS:
How They Interface

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ECS and FDA Inspections

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (Biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

In this issue, we discuss ECS and what part they may have in a Food and Drug Administration (FDA) inspection. One early note: in this article we use the FDA's term, FDA Inspection, but you may think of it as FDA Auditing. The terms are essentially interchangeable.

Introduction

When it comes to ECS, many product vendors spout out a near endless alphabet soup of compliance claims: HIPAA, Sarbanes-Oxley, 21 CFR Part 11, and ISO-15489, along with many others. Sorting out what is significant and what isn't will be helpful to those who have or will purchase and use ECS products. For instance, there is a difference between mandatory and optional compliance. Compliance with all *laws* and *regulations* is mandatory; compliance to *standards* (such as ISO-15489) is optional.

At heart, an FDA Inspection is meant to ensure regulatory compliance. What many in the Biopharma industry do not realize is that when it comes to regulatory compliance, it is the business (and its staff) that needs to be in compliance, not the ECS vendor's products. Despite claims by vendors stating their products are compliant, they are not. The products can only contain functionalities (e.g., features) that help a business attain compliance. It is up to the business to ensure that the functionalities provided by the vendor's product(s) are implemented and used in such a way that the business is in regulatory compliance.¹

In this issue, we discuss the FDA mandate, and the regulations that have been developed to help the FDA meet its mandate. Further, we review some of the deficiencies that have prompted FDA warning letters. Next we discuss what Biopharmas need to do in order to show compliance, and in particular, we discuss the compliance aspects of ECS. Lastly, we offer suggestions as to how Biopharmas can determine if they are ready for an FDA inspection, and discuss what one might expect during the inspection.



FDA Mandate and Regulations

The FDA was created to make sure that only safe and effective drugs are on the market. In order to accomplish this, the FDA has formulated a number of regulations; most important of these, insofar as ECS use is concerned, are the collection of regulations known as “Predicate Rules,” which consist of Good Practices that cover a number of areas such as Manufacturing (GMP), Laboratory (GLP), and Clinical Trials (GCP). Other regulations, such as 21 CFR Part 11, refer to the Good Clinical Practice regulations. For an overview on regulations and compliance, see Issue 3 of *EDC Today, Regulations and EDC: Assuring Compliance*.² For an in-depth look at the GCP regulations, see the FDA website, <http://www.fda.gov/oc/gcp/regulations.html>.³

In summary, the basic tenets of these regulations as they relate to the FDA Mandate are shown in Table 1.

Table 1. Basic Regulatory Tenets

Make sure clinical data is objective.
Make sure clinical study is unbiased.
Make sure clinical data is not changed to make the results of a clinical study look better; that is, to prevent fraud.
Make sure only authorized people are making changes to clinical data.
Make sure people working in clinical trials are trained to perform the work they perform.
Make sure processes are documented and followed to insure reproducible conclusions.

FDA Warnings

Deficiencies found in FDA inspections are communicated in the form of a warning letter. If you receive a warning letter, you should respond with a letter indicating what steps you are taking to correct the deficiencies.

The FDA posts these warning letters on its website and it is informative to see what sort of deficiencies the FDA has noted, especially any that could apply to you! The letters can be found at <http://www.fda.gov/cder/warn/index.htm>⁴ and are organized by year. Deficiencies of recent warning letters are shown in Table 2.

Table 2. Recent Warning Letters

Misleading or inaccurate product advertising or labeling.
A site that used a single shared login account to do all its work with a software application.
Software that was missing an audit trail altogether!

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Achieving Compliance

It is important to note that the FDA is not an adversarial organization. But they do want to make sure Biopharmas are following the regulations. Table 3 shows deficiencies an FDA auditor is trained to look for.

Table 3. Deficiencies looked for by an FDA auditor (based on an aggregate of reported deficiencies)

Inadequate Patient Consent Form(s)
Failure to Adhere to Protocol
Inadequate and Inaccurate Records
Inadequate Drug Accountability
Failure to Keep Institutional Review Board (IRB) Informed of Protocol Changes ⁵

Obviously, not all of these items involve ECS (or do so indirectly.) What you might evaluate, however, is how your ECS solution supports acquiring proper patient consent forms. Is there an information portal available with instructions for the investigator to follow? Does the portal provide investigators and in-house personnel access to the protocol and any amendments? Are protocol violations found and addressed quickly? Does your ECS solution flag violations and bring them to the attention of everyone that needs to know about them? Inadequate and inaccurate records cover far more than just clinical trial data records. One can begin with these records, however, and develop documentation that shows that they are both adequate and accurate – by validating the ECS system and the systems developed to capture the clinical trial data. Other data, such as study management records, investigator site records, training and even staff qualification records all need to be adequate, accurate and organized! Lastly, your ECS system may have functionalities that support drug accountability. If so, you should document who uses these functionalities and how they use them.

ECS Considerations

System Validation and Security

Like regulatory compliance, system validation of an ECS product is a Biopharma's responsibility, not the ECS vendor's. The software will need Operational Qualification (OQ) and any clinical trial (i.e., protocol) specific application will need to be validated. Validation shows that the system performs as expected and ensures that the generated records are adequate and accurate. Furthermore, any data derivation or transformation will need validation that bears close inspection.

Securing your system (from unauthorized use and/or change) and the data stored within it is important, perhaps even more so when you use electronic records. Servers should be behind locked doors. Databases should require passwords; access to data should be restricted as completely as is practical. Passwords need to be changed periodically. No one should have passwords written down on a post-it stuck to the monitor! (Believe it or not, this was issued in an FDA warning!)

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One thing we would like to highlight about 21 CFR Part 11, “Electronic records and Signatures”: if you are using electronic signatures, there should be a password policy to ensure the signature is authentic and truly belongs to the “signer”.

System Audit Trail

In short, you probably need to be able to generate a report that shows a data element from “creation” to “current” that shows: who entered/edited/deleted it, when the action took place, why the action took place, and before and after data values. Your ECS vendor’s product should provide this. What you need to demonstrate is that the “who” is the user that logged in (and no one else); the “when” is a computer generated date-time stamp (with some caveats about trying to ensure the user doesn’t alter their computer clock and that that clock is reasonably “accurate”), the “why” is a user supplied reason for change, and the before and after change values are accurate.

The burden of “automatic computer-generated audit records” is that the user can NOT modify the audit trail outside of the ECS application and can ONLY access the audit trail information via a report if they are privileged to do so. You need to do what you can to ensure the user is who they say they are (i.e., have password life cycles and policies in place), doing what they claim to be doing, when they claim to be doing it.

User Training

An important part of compliance is showing that the people involved in your process are trained and qualified. Documenting both training and qualifications is important. Web-based training covering the ECS application and/or the clinical trial might be available that would assist you with achieving compliance in this area.

User training should cover processes and SOPs, as well as software applications. It is important that all employees be knowledgeable about the SOPs that affect the work they do. The only way to insure repeatability when different people do the same work is for both people to follow the exact same procedures.

Reports

All information reported to the FDA (e.g., Safety reports) needs to be reproducible. Reconstructing a report may be difficult if the database/datasets underlying the report is not archived/snapshot along with the software that generated the report. Having a change control process only partially addresses this – there needs to be an archive control process too.

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Determining Inspection Readiness

If you don't think you are ready, chances are you are not. A quick list of things to consider follows. Can you answer "yes" to these questions?

- Do you follow GCP?

Following GCP is not optional - it is the law. Do you know what predicate rules govern your day-to-day activities? Do you know which Standard Operating Procedures (SOPs) cover your day-to-day activities? Have the computer systems you use day-to-day been validated?

- Are your site files and documentation in good order and up-to-date?

This documentation should include (but isn't limited to) such items as regulatory documents, adverse event and safety data, study management files (e.g., written letter and e-mail communications, drug accountability, informed consent forms, call logs), investigator files, previous audit reports and follow-up.⁶

- Do you have, and follow, SOPs?

It is important to establish documentation of personnel involved, the degree of delegation of authority, locations where specific aspects of the study were performed, how and where the data were recorded, and protocols for maintaining study agent (drug) accountability. Specific to ECS, documentation establishing the validity of electronic signature, password policy, and complete records of system validation is essential.

- Who is accountable?

The individual (or team) who is accountable for performing the tasks that need to be done in order to get your drug to market must be clearly identified for the inspector.

- Do you document your training and qualifications?

Attendance should be kept at training sessions such as investigator meetings or equivalent, specialized site training, Drug Information meetings, and other seminars. Staff curriculum vitas (resumes) should be on file and kept up-to-date.

What to Expect in an FDA Inspection

Knowing whether or not you are ready for an FDA Inspection is difficult. What is certain is that there is a lot of preparatory work that needs to be done. Regulations are complicated and hard to understand. They can even seem contradictory at times. Fortunately there are lots of resources available. There are a number of books in print and an even larger number of companies that give training seminars in how to prepare for an FDA inspection. It comes down to knowing the law and regulations and doing what you need to do in order to become, and remain, in compliance.

There is one thing to keep in mind. The only way the FDA inspectors can determine if a company is in compliance is by the quality of the company's documentation. It is one thing to say you are following SOPs. However, without some kind of paper trail that shows you are actually following your SOPs, there is no way for the FDA to see proof that you are following them. Therefore, it is important for you to acquire and maintain signoffs and other documentation as each process is executed.

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Conclusions

An FDA Inspection is meant to ensure regulatory compliance. The role of the FDA is not to be needlessly adversarial, but rather to ensure that safe and effective medicines are approved.

Compliance with all *laws* and *regulations* is mandatory; compliance to *standards* is optional. It is the business that needs to be in compliance. ECS vendor products of themselves are not compliant; they can only help a business to be in (or out of) compliance.

Knowledge and understanding of applicable regulations is essential. Everyone in the Biopharma industry should be trained in all the good practices that are applicable to their work. And documentation of this training is necessary.

Good, complete, organized documentation is critical. The only way the FDA can see that you are in compliance and following your procedures is to view the records that document it.

Taking the time to do what needs to be done to be in compliance is critical to “passing” an FDA inspection.

References

¹ Julie Gable, “Information Life Cycle - Compliance Simplified”, *Transform Magazine*, Vol. 13, No.2, February 2004.

² EDC Today™, Issue 3, “Regulations and EDC: Assuring Compliance”

³ <http://www.fda.gov/oc/gcp/regulations.html>

⁴ <http://www.fda.gov/cder/warn/index.htm>

⁵ Perkins and Perkins, “The FDA is Coming to Audit Your Clinical Studies”, white paper, <http://www.perkinsandperkins.net/PosFr2.html>

⁶ Sue Nunchuck, “Preparing for Regulatory Audit”, *The Investigator*, May 2002.



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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