WHITE PAPER

Data Integrity and CSV Compliance Solutions for Drug Manufacturers

Introduction

The term "data integrity" refers to the completeness, consistency, and accuracy of generated data. Ensuring data integrity in drug manufacturing operations is not a new concept - it has been part of the pharmaceutical industry landscape for many decades. What is new, comparatively speaking, is data integrity protocols for today's highly digitized workflows. Beginning in the 1990s, the integrity of electronic data and systems has moved to the forefront with researchers, manufacturers, and regulators.

A computer system is a set of software and hardware components that is used for a specific purpose. When data is generated, recorded, and stored by a computer system during research or production, the computer system becomes part of the data integrity compliance efforts of drug manufacturers. Hence, the term "computer system validation," or CSV, is often mentioned in tandem with data integrity.

Effective data governance programs for drug manufacturing operations will contain many of the same basic components across the industry. Regulatory requirements for such vary from country to country.

Here, we review the data integrity and CSV regulatory setting in the United States (US) and the European Union (EU), discuss some of the trends and challenges drug manufacturers face, and identify best practices to help them succeed in their data integrity compliance efforts.

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Agencies and Regulations

In the EU, Annex 11 [1] is a supplement to the broader good manufacturing practice (GMP) rules for medicinal products published by the European Commission's Health and Consumers Directorate-General. Annex 11 focuses on data integrity in the use of computerized systems as well as the personnel and third parties involved with that use. The practices of Annex 11 do not have the force of law, but they are strongly recommended to ensure electronic data integrity is achieved and maintained.

In the US, the federal Food and Drug Administration (FDA) uses the rules in 21 CFR Part 11 [2] to evaluate and enforce data integrity requirements for electronic records and signatures in drug manufacturing operations. Part 11 defines an electronic record as:

"any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system."

and an electronic 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."

Although Part 11 focuses specifically on electronic records and signatures, in practice it is part of the broader good manufacturing practices (GMP) stipulated in 21 CFR Part 211. [3] For example, Part 11 and Part 211 dovetail in their data integrity criteria: attributable, legible, contemporaneously recorded, original, and accurate, commonly known as ALCOA.

Part 11 also overlaps with 21 CFR 312.23(7) concerning the data integrity of chemistry, manufacturing, and control (CMC) information required for investigational new drugs before they can enter clinical trials. [4] These overlaps are not surprising given that Part 11, Part 211, and Part 312 rules are each focused on human safety.

FDA Viewpoint of Data Integrity

The last several years have witnessed the FDA increasing their scrutiny of the data integrity and CSV programs of drug manufacturers. Understanding how the FDA views and evaluates data integrity is critical for manufacturers and laboratories in order for them to maintain compliance and avoid penalties.

An FDA data integrity inspection of a drug manufacturing facility focuses on one or more of the key elements of Part 11:

1. Computer systems validations
2. Computer- generated, time-stamped audit trails
3. Compliance of "legacy" systems that were operating before Part 11's effective date of August 20,1997 but have been subsequently modified
4. Ability for FDA to inspect, review, and copy records
5. Proper records retention based on "a justified and documented risk assessment and a determination of the value of the records over time."

When inadequacies are noted, the FDA issues a letter to the company detailing the violation(s) found. When there is no potential for a violation to cause adverse human health effects, FDA provides a timeline for the company to complete and report their remedial actions.

FDA acts swiftly and harshly in response to violations that could result in adverse human health effects from use of the drug product. Major violations such as practices that have resulted in contaminated products, adverse reactions in users, egregious gaps in a data quality program, and others can result in manufacturing shutdown, product recall, or other serious consequences, including hefty fines.

The FDA maintains a database of their inspection findings and conclusions, which can be helpful for manufacturers in compliance planning and program review. It is not uncommon for FDA to increase inspections for violations that are noted to be on the increase. The agency sometimes issues guidance documents in order to help manufacturers better understand and comply with trending problems.

In addition, two general guidance documents issued by FDA to help the industry meet data integrity requirements are:

- Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application
- Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry

Data Integrity Considerations and Trends

Data integrity programs must cover the full data lifecycle, from data generation and analysis to archiving and destruction. One of the most challenging compliance points in that lifecycle is at the end-of-life for hardware or software. The data must be archived or migrated to a new instrument or system, which can be difficult when the components do not easily integrate with each other. Preparing for these inevitable transitions should be an important part of a company's instrument and software continuity planning and data integrity program.

The pharmaceutical industry and related professional organizations have been increasing their efforts to develop guidance documents for industry-wide data integrity and CSV needs. For example, the US Pharmacopeia (USP) has recently updated its Chapter <1058> on analytical instrument qualification, to include testing of software functions to verify system data integrity.

Drug manufacturers and laboratories are conducting more thorough evaluations when selecting instrumentation and software. In addition to price point and performance capabilities, they are looking for data integrity and CSV competencies that will help them meet or exceed security requirements and maintain complete audit trails, among other data integrity considerations. In response to these demands, hardware and software companies are integrating data integrity considerations into their new or updated products.

A growing trend within the drug manufacturing industry is the creation of corporate data integrity governance programs. Such programs provide a dedicated focus on data integrity and CSV compliance throughout the company and are critical for successful compliance and avoidance of violations, fines, or worse.

Best Practices for Data Integrity Success

A drug manufacturer is well-served by having a data integrity governance committee and a data integrity manager who has the knowledge, authority, and dedicated time needed to oversee the program. The committee and manager must work together to develop well-defined data integrity policies and practices, including routine data integrity assessments. The data integrity manager must have ownership of implementing, monitoring, and adjusting those policies and practices as needed over time, with committee input.

The expertise and experiences of other organizations can be very helpful when developing a data integrity program. The committee and manager should seek out information available from professional organizations, industry guidance, government guidance, trends reports, and so forth. The data integrity manager should regularly monitor such sources for new information that might be helpful in adjusting or improving their company's program.

Proactive partnerships with other organizations in the broader industry can help a drug manufacturer optimize their data integrity program. Organizations such as materials and technology providers, who must keep their fingers on the industry pulse to better serve their own customers, can be an invaluable source for leading-edge input and support.

Conclusion

Data integrity compliance has become a large and crucial part of drug manufacturing operations. The pharmaceutical industry and professional organizations are ramping up their efforts to address and standardize data integrity needs and processes. Concurrently, individual companies are putting more dedicated resources into their data integrity and CSV programs. These multi-pronged efforts will serve the industry, and their customers, well into the future.

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