FDA Increasing Scrutiny of Data Integrity and Compliance with cGMP

By Rob Sims/UL EduNeering | June 3, 2016

Data integrity, as it relates to drug development and manufacturing, is one of the FDA's top enforcement priorities. Defined as the completeness, consistency, and accuracy of data that is attributable, legible, contemporaneously recorded, original or a true copy, and accurate, data integrity is currently one of the most relevant topics in quality management. It is also mandatory for Life Sciences companies since "Assumptions on product quality and compliance with the applicable regulatory requirements are made based on data."[1]

Properly recorded, reported, and traceable information is essential for companies to offer proof that their products have been manufactured in line with established protocols, and to assure their identity, quality, strength, purity, and safety before market distribution. This digital audit trail, compliant with FDA 21 CFR Part 11, establishes the criteria under which electronic records and signatures are stored.

Global consumers have an expectation that the drugs they take are safe, authentic, and effective. To protect the public health, and uphold the public trust, the FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency, and the Indian Food & Drug Administration, among other regulatory bodies, have established standards commonly referred to as current Good Manufacturing Practices (cGMP). The "current" is to remind manufacturers that they must deploy and maintain up-to-date systems and technologies to remain in compliance with evolving regulations.

However, the growth and globalization of the industry has put downward pressure on attempts to regulate it. Over the past few years, data integrity has emerged as a more serious compliance issue at pharmaceutical manufacturing plants. As FDA on-site inspections of systems and processes at overseas facilities increase, so has the incidence of data ma-nipulation, document adulteration, and other cGMP infractions in India, China, and other international markets. Data integrity concerns are well documented in India. Since 2013, the FDA has cited at least 15 companies over the consistency and accuracy of their data. Some of the more serious violations found companies lacked the facility to backup and restore data, allowed laboratory analysts to share Login IDs, and backdated lab data.

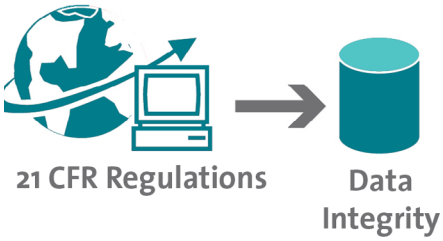
The Regulatory Affairs Professional Society reported in April 2016, that FDA inspectors visiting a facility in the city of Bangalore discovered major instances of misconduct and violations, including the substitution and manipulation of study subject samples. And the FDA is not acting alone. Both the European Medicines Agency and the World Health Organization have targeted Indian manufacturers for data integrity deficiencies.

In China, FDA inspection teams have discovered circumstances where sample raw data file names were changed, and audit trails disabled. According to Bloomberg, during a recent visit to a pharmaceutical factory in the Chinese city of Taizhou, FDA inspectors noticed that when workers conducted quality tests on drugs for U.S. export, they sometimes didn't record the results, and at other times, deleted them. Some of these violators found themselves placed on an import ban list that prevented them from shipping products to the U.S.

Manufacturers who fail to take satisfactory corrective action may be served with a Form 483, a warning letter, import alert, or other penalty. "These regulatory actions not only impact the revenue stream of the company, but also affect the drug maker's ability to get approval for new drug applications." [2] The outcomes from cGMP violations can be severe, from loss of business to reputation damage to competitive disadvantage, as rivals are poised to turn misfortune into opportunity to increase their market share.

In response to the spike of incidents recently observed during cGMP inspections, in April 2016 FDA's CDER Division published a question-and-answer Draft Guidance titled Data Integrity and Compliance with CGMP Guide for Industry.

Key regulations cited by FDA investigators are provided below:



211.68(b) – appropriate controls must be exercised over computer or related systems to assure that only authorized personnel institute changes in master production and control records

212.110(b) – data must be "stored to prevent deterioration or loss"

211.100 and 211.160 – activities must be "documented at the time of performance" and that laboratory controls be "scientifically sound"

211.166(a) – stability testing results must be evaluated to determine appropriate storage conditions and expiration date

211.180 (d) – stored records must be "original records" – for example, a printed paper copy of the chromatogram is not a "true copy" of the entire electronic raw data used to create that chromatogram

211.188 and 211.194 - information must be "complete data derived from all tests" and "complete records of all tests performed"

This document provides some initial insights into FDA expectations, and what companies can do to meet them. The intent is to clarify the role of data integrity in cGMP as required under 21 CFR parts 210, 211, and 212. Several of its recommendations include 1) the disclosure to the FDA of data integrity violations, and the removal from cGMP positions at all levels of those individuals responsible for them, and 2) that Quality Assurance review all audit trail and electronic testing prior to batch release.

While not binding, the FDA does tend to rely on Draft Guidance during inspections and in making enforcement decisions. "The guidance essentially sets up data integrity measures that drug manufacturers can ignore only at their peril, measures that go beyond what the regulations require."[3] The 21 CFR Part 211 protocols emphasized in the document form an integral part of FDA data integrity standards, and require that:

- **Backup data is exact, complete, and secure from alteration, inadvertent erasures, or loss.**
- **Data be stored to prevent deterioration or loss.**
- **Certain activities be documented at the time of performance and that laboratory controls be scientifically sound.**
- **Records be retained as original records, true copies, or other accurate reproductions of the original records.**
- **Complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.**

Life Sciences organizations seeking a prudent strategy to synchronize data integrity with cGMP should start with effective education. "It's about getting back to the roots of training all staff on the importance of data integrity in cGMP documentation and honesty. It is critical to ensure employees understand the accountability and traceability requirements for retention of raw data and the consequences of data manipulation."[4]

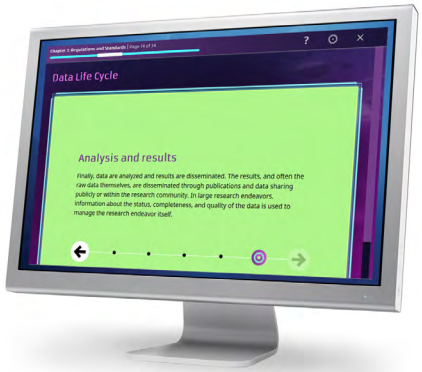
Quality and competency training, however, comes with its own bumps and warts as data integrity issues often are embedded in corporate culture. Recent Ernst & Young research, for example, revealed "While the company may hire the best international trainers, employees mentioned that there were language and accent barriers which prevented employees from understanding the content, thereby making the training redundant."[5]

"The FDA expects that data be reliable and accurate."[6] By ratcheting up their scrutiny, the FDA and other global regulators are sending a message that they take data integrity and good documentation practices seriously. Organizations should be prepared to implement meaningful and effective strategies to manage their data integrity risks.

Staying off the regulatory radar requires a quality approach to manufacturing. Companies operating in the Life Sciences space must see to it that effective controls and oversight are implemented in advance of inspections. Every effort should be made to ensure the accuracy and reliability of data so instances of contamination, mix-ups, and errors can be eliminated, and consumers are protected from buying products that are either ineffective, or hazardous to their health.

New Data Integrity Program

UL's new Data Integrity eLearning program enables a company to educate a wide range of lab and manufacturing workers on key issues related to data integrity: record-keeping, documentation, how to prevent falsifying records, etc. Currently there are two main eLearning courses, one that provides a Data Integrity introduction to all employees, and one focused on issues that impact IT professionals. Throughout 2016 UL will introduce additional Data Integrity "modules" targeted to specific workers: lab workers, manufacturing workers, and clinical workers.



References:

1 Source: Schmitt, Siegfried, Data Integrity: FDA and Global Regulatory Guide, Parexel Consulting, 2015.
2 Source: Analyzing the State of Data Integrity Compliance in the Indian Pharmaceutical Industry, Ernst & Young, 2015.
3 Source: Ibid. 1.
4 Source: Best, Elayne, Data Integrity Issues: Causes and Solutions, Parental Drug Association, pda.org, March 30, 2015.
5 Source: Schwartz, Mark L., and Farquhar, Douglas B., FDA's Draft Guidance on Data Integrity: The Cupola on a Tower of Guide-lines, FDA/Law Blog, April 17, 2016.
6 Source: Data Integrity and Compliance With CGMP Guidance for Industry – Draft Guidance, US Food & Drug Administration, April 14, 2016.

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