DATA INTEGRITY AND WARNING LETTERS

Data integrity remains a hot topic in the pharma biotech industry—and the trend has only been gaining steam. Within the past 10 years, the volume of data integrity-related warning letters has increased dramatically. In 2016 alone, new guidance documents were released by the U.S. FDA, Medicines and Healthcare product Regulatory Agency (MHRA), European Medicines Agency (EMA), Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the World Health Organization (WHO). Yet despite these efforts, companies continue to struggle with data integrity issues.

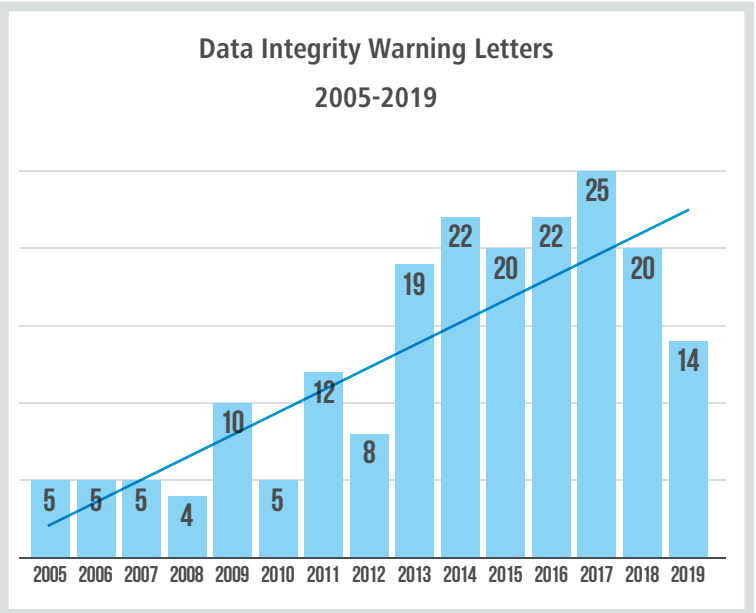

Figure 1

Based on the number of warning letters issued between 2005 and 2019 that cited data integrity deficiencies **(see Figure 1)**, FDA enforcement has been ramping up. It is no fluke that a clear uptick began after 2010. This is when the FDA began incorporating data integrity into its pre-approval inspection (PAI) process, making it one of the primary inspection objectives in the FDA's Compliance Program Guidance Manual 7346.832. Other contributing factors to this trend include better training for inspectors, incorporating data integrity as an inspection objective, and companies not having robust systems and controls over computerized inspection equipment.

WHAT ARE THE MAIN ISSUES RELATED TO DATA INTEGRITY?

At NSF International, our extensive data integrity research looked at our own clients, the newest guidance documents and regulatory enforcement actions. To see where companies struggled the most, NSF reviewed warning letters from 2005 through 2019 that addressed data integrity deficiencies. We then grouped the deficiencies into themes and what we found was quite revealing **(see Figure 2**).

HIGHLIGHTS OF THE FINDINGS

Topping the list was the theme of **incomplete or missing records.** This was cited 131 times in 196 warning letters **(67%)**. An example of an incomplete or missing record is data that was processed multiple times but only had one data set present. Other examples include injections in a sequence not included in the data package, missing flasks, solutions or microbial test plates for tests that are supposed to be in process and missing data that would support analytical results.

The theme of access control deficiencies was cited 61 times **(31%)**. These deficiencies include users having inappropriate privilege levels, such as administrator rights, and systems having inadequate controls that allow users to modify results or delete files.

Deleting or destroying original Good Manufacturing Practice (GMP) records was a theme cited 49 times **(25%)**. Citations included analysts deleting data on electronic records as well as finding sample notebooks and test records in the trash.

The theme of reintegration, reprocessing and inappropriate manual integration was cited 45 times **(23%)**. This includes instances where samples are reprocessed multiple times with no justification and only one set of data was reported. It also includes excessive manual integration with no justification or procedure to define the practice.

With 43 citations **(22%)**, **audit trail deficiencies** rounded out the top five themes. Audit trail issues run the gamut from systems without audit trail capability and audit trails being disabled by users, to audit trails not being reviewed to detect deletion or manipulation of data.

WHAT ARE SOME CONSEQUENCES OF DATA INTEGRITY-RELATED FINDINGS?

Data integrity findings are taken very seriously by the FDA. Deficiencies can erode the trust between the FDA and a company, resulting in FDA 483s, warning letters, import alerts, injunctions and in extreme cases, the FDA invoking the application integrity policy. Not surprisingly, the FDA is getting more aggressive with enforcement. In the past four years, it issued 39 import alerts. In the 11 years before that, only three import alerts were issued for data integrity issues. The three "heavy hitters" most likely to elicit an import alert are falsifying data, deleting original GMP records and using methods that are not validated.

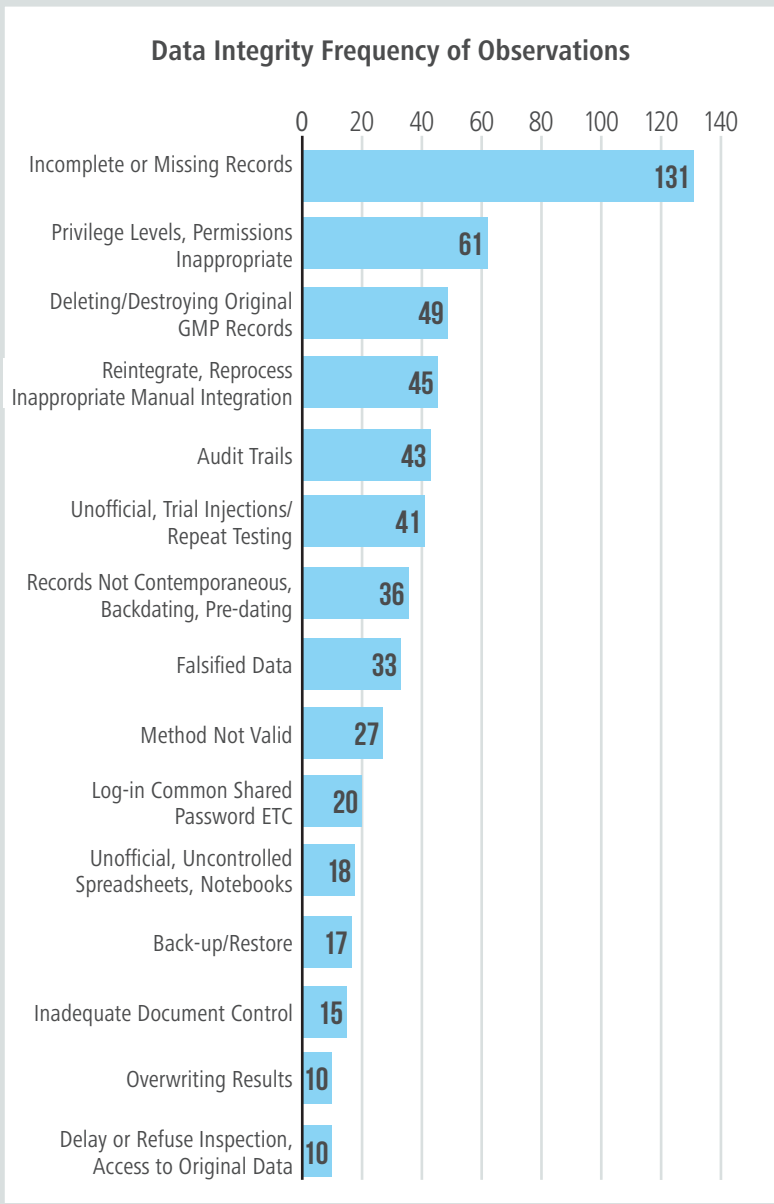

Figure 2

FDA RECOMMENDS THIRD-PARTY CONSULTING SUPPORT

The FDA has increasingly recommended that companies reach out to a qualified third-party consultant to help address certain data integrity issues **(Figure 3)**. NSF has served as an independent third-party on many such occasions and is recognized as an expert in this role.

WHAT CAN COMPANIES DO?

When thinking about data integrity and data governance, companies should first evaluate the entire data lifecycle. Secondly, companies should take a risk-based approach to addressing data integrity concerns, factoring in data criticality and data risk. The level of effort to mitigate data integrity gaps should be commensurate with the risk present at the time.

At NSF, we have seen many companies move along the data integrity maturity curve from initial awareness and basic understanding to ultimately implementing robust data governance programs. Most clients first come to us struggling with the application of data integrity concepts. They often ask such questions as:

- Do I need to review audit trails?
- How often do I need to review them?
- And what in particular should we be looking at?

NSF has helped many clients answer these questions, putting into action simple yet comprehensive solutions. If you feel that your company could use some help implementing data integrity controls, contact us at **healthsciences@nsf.org** to discuss how we can meet your needs.

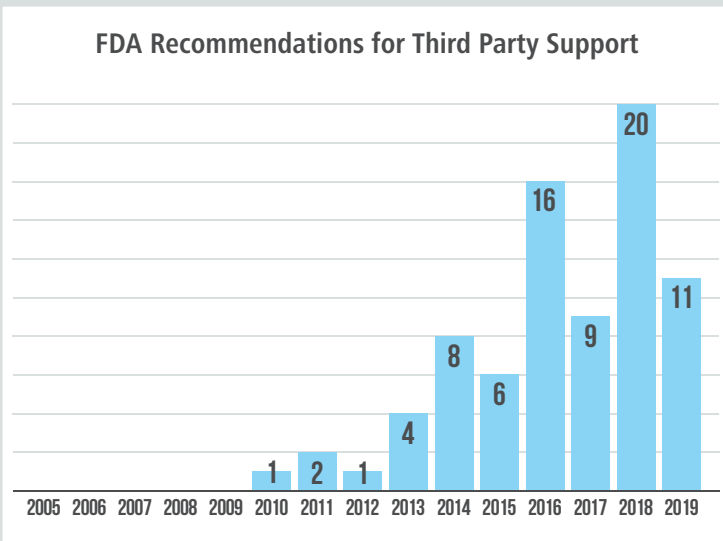

Figure 3

ABOUT THE AUTHOR

Maxine Fritz has 30+ years of combined FDA, industry and consulting expertise and is responsible for overseeing the Pharma Biotech practice at NSF International, serving in both a technical and management role. Ms. Fritz works with clients in the pharmaceutical, biologics, biotech and medical device industries to develop quality assurance, manufacturing and regulatory strategies for compliance with FDA regulations. She conducts and oversees regulatory gap analyses, assists with the development and implementation of quality systems, and develops and implements corrective action plans to address deficiencies identified by regulatory agencies. Ms. Fritz has successfully managed, resolved and consulted on large complex compliance projects including corporate warning letters, mass seizure, consent decree(s), Application Integrity Policy (AIP) prosecution and import detentions.

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