DATA INTEGRITY:

How to Prevent a Significant Source of 483s and Warning Letters in Drugs, Devices, and Biologics

5 Practical Ways to Proactively Avoid Data Integrity Issues for Improved Quality

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Beyond Procedural Deficiencies: The State of 483s and Data Integrity

Pharmaceutical and biotechnology companies are no strangers to FDA 483s and warning letters. The categories of Devices and Drugs accounted for the second- and third-most 483s issued by the FDA in 2019, behind only Food.[1]

While "lack of or inadequate procedures" and similar procedural deficiencies were the most frequently cited issues in 2019 for Devices and Drugs, data integrity was responsible for a significant portion of 483s in these categories as well as in Biologics, which ranked sixth on the list in 2019.[1]

Issues related to data integrity accounted for roughly 19.8% of all 483s in the Devices category in 2019, 14.7% of 483s in Drugs, and an overwhelming 41.3% in Biologics.[1] Although data integrity is not the top source of 483s, it is an area that deserves a high level of attention by quality and validation teams and can have a major impact on quality in these biopharma and biotech sectors.

	Devices	Drugs	Biologics
# of 483s Related to Data Integrity Issues	621	547	95
% of 483s Related to Data Integrity Issues	19.8%	14.7%	41.3%

Figure 1. 483s issued by sector, based on data from the FDA Inspectional Observation Data Set for FY 2019.[1]

In other words, the 483s will not be relenting. Companies that can identify, remediate, and prevent data integrity issues will have a distinct advantage over those that continue to let data and procedures go unchecked.

Warning Letters Increasing in Volume and Speed

The FDA is getting faster and nimbler with warnings—not only delivering on the promised crackdown of quality control issues at manufacturing facilities abroad—but improving their efficiency in the United States.

Figures 2 and 3 show that the FDA's time to issue a warning letter after an inspection has shortened while the number of warning letters issued has increased.[2]

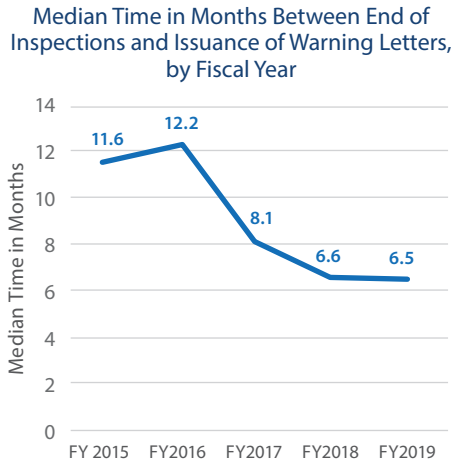

Figure 2. The FDA achieved an overall 44% improvement in median time between the end of an inspection and issuance of a warning letter from FY 2015 to FY 2019. Source: fda.gov[2]

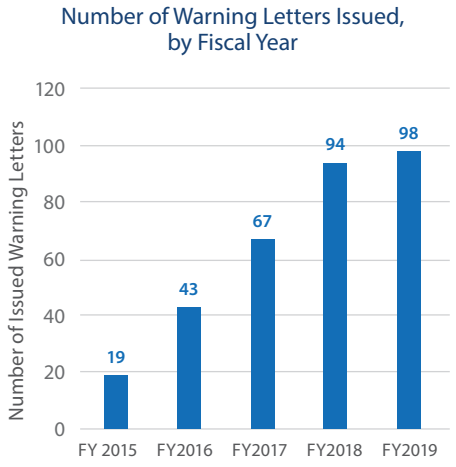

Figure 3. The number of warning letters issued by the FDA increased from 19 in FY 2015 to 98 in FY 2019. Source: fda.gov[2]

5 Ways to Address Data Integrity and Process Issues to Minimize 483s and Warning Letters

Most Common 483s Related to Device History Records[1]

DHR – not or inadequately maintained: A device history record has not been [adequately] maintained.

DHR content: The device history record does not demonstrate that the device was manufactured in accordance with [the device master record] [21 CFR 820].

1. Get Strict About Maintaining Device History Records

For medical device manufacturers, DHRs are a top source of 483s related to data integrity.

According to the FDA's Code of Federal Regulations, Title 21, Part 820 on Quality System Regulation (21CFR820.184):

> *"Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include, or refer to the location of, the following information:*
>
> *(a) The dates of manufacture;*
> *(b) The quantity manufactured;*
> *(c) The quantity released for distribution;*
> *(d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR;*
> *(e) The primary identification label and labeling used for each production unit; and*
> *(f) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used."* [3]

An accurate historical record of your device risk assessment activities is a must to verify the quality production of all parts of the device as specified in the device master record. It will also help you identify and track devices throughout the manufacturing and supply chain, which is critical when investigating errors and nonconformance.

Designating a single point person to update the DHR on a rolling basis as updates are made can prevent a backlog of changes and subsequent warnings.

A regularly scheduled interval may be more feasible for your team than real-time updates. Whatever cadence you decide on, be sure one person is responsible and held accountable for making the updates.

When it comes to manufacturing the device, you can avoid 483s by simply following the procedures outlined in the DHR, which will be much clearer to those carrying out the manufacturing process if you keep the DHR up to date.

If you're still working with paper, consider upgrading to a digital QMS document control system to prevent lost paper documents and filing errors while also enabling quicker and easier documentation updates.

Most Common 483s Related to Document Control[1]

Documentation: Corrective and preventive action activities and/or results have not been [adequately] documented.

Procedures not adequately established or maintained: Document control procedures have not been adequately [established] [maintained].

Lack of procedures, or not maintained: Document control procedures have not been [established] [maintained].

2. Establish Clear, Specific Document Control Procedures Across the Board

While this is more of a procedural issue, lack of attention to good documentation practices leads to data integrity issues down the line. Many pharmaceutical and medical device manufacturers could be well-served to remember that GDP are not recommended best practices; they are legal requirements.

As a refresher, be sure your documentation methods are compliant with ALCOA:

- **Attributable:** Information of the signer is duly captured in the records, and is uniquely verified with a full robust authentication mechanism.
- **Legible:** Documents stored are readable, understandable, and allow complete tamper proof details of the user who signed or reviewed the document and many other considerable actions.
- **Contemporaneous:** This is the record at the time data is generated.
- **Original:** Data in the form in which it was originally generated.
- **Accurate:** Correct, truthful, complete, valid, and reliable data.

Following GDP can also help your organization attain important ISO and other industry certifications to verify compliance with good manufacturing practices.

If your organization is struggling to meet GDP requirements, consider the following:

Establish and define a document control process not just for SOPs, but for batch records, change control, and validation documents. A well-defined documentation control process will ensure all employees receive the latest versions and that documents are reviewed and revised at appropriate intervals.

Identify and specify overly vague standard operating procedures. With some pharmaceutical companies having more than 1,000 SOPs, the revision process can be daunting but will pay off in the long run. If every employee cannot clearly understand and repeat an SOP step-by-step without fail, it needs to be rewritten for clarity, with specificity, or to add updated information.

Address training deficiencies. Document control issues are often correlated with employee training shortcomings. Avoid human error by implementing a strictly followed SOP training process, reporting hierarchy, and periodic retraining program to correct and prevent deviations.

3. Establish a Reliable Vendor Audit Program

When it comes to ensuring data integrity, suppliers and vendors are just as likely as internal team members to be the source of critical issues. That's why stringent vendor audit programs are a must.

The APIC Supplier Qualification & Management Guideline recommends vendor assessments and audits commensurate with the material supplied.

Requirement	Non-Critical Raw Material	Critical Raw Material	Registered Intermediate / API
TSE / BSE Assessment	✓	✓	✓
Tanker Cleaning Assessment	✓	✓	✓
Supplier / Manufacturer Questionnaire	✓	✓	✓
Manufacturer Audit		**✓	✓
Historical Performance	**✓	✓	✓
cGMP Compliance History		**✓	✓
Third-Party Certification	**✓	**✓	✓
Contract Agreement	✓	✓	✓
Quality Agreement		**✓	✓

✓ Required **✓ Dependent on risk assessment performed on material being purchased

Figure 4. Summary of quality assessment procedures. Source: Active Pharmaceutical Ingredients Committee[4]

Requirements given to outside vendors are often too general, incomplete, or outdated. To prevent vendors from creating data integrity issues inside your organization, review and revise your current vendor audit guidelines to include specifics like:

- **Security:** Measures for cloud-based systems to prevent hacking
- **Accessibility:** Shared password and login protocols and control management
- **Accuracy:** No errors or editing without documented amendments
- **Attribution:** Information lists who acquired the data or performed an action and when
- **Availability:** For review and audit or inspection over the lifetime of the record
- **Completeness:** All data is present and available

Most Common 483s Related to Batch Records[1]

Prepared for each batch, include complete information: Batch production and control records [are not prepared for each batch of drug product produced] [do not include complete information relating to the production and control of each batch].

Written record of investigation incomplete: Written records of investigations into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications] do not [always] include the conclusions and follow-up.

Batch production and Batch Control Record Requirements: The batch production and control records are deficient in that they do not include documentation of the accomplishment of each significant step in [manufacturing] [processing] [packaging] [holding].

4. Invest in Electronic Batch Records Software for Faster, More Accurate Recordkeeping

Following GDP, providing proper training to field employees, and improving QA review processes can help to control batch record errors—but as long as batch records are done manually on paper, errors will abound.

Despite the availability of electronic systems, paper-based batch records management is still the norm in the pharmaceutical industry. Paper processes are cumbersome and prone to inevitable human error. Physically recording, reviewing, and auditing on paper takes vast amounts of human hours to work on batch records that are often hundreds of pages long.

This high volume of paper handling inevitably leads to illegible entries, incorrect data, missed fields, transcription errors, lost paper, and a host of other data integrity issues.

What's worse, the overwhelming volume of paper-based records encourages QA teams to take shortcuts to get batches out the door on schedule, which creates many openings for data integrity issues.

Fortunately, electronic batch records software offers a streamlined alternative to manual paper processes. EBRs can:

- Prevent invalid entries
- Limit backdating
- Prevent incomplete form submissions
- Achieve 100% right-first-time rates
- Streamline auditing
- Instantly query batch records
- Improve quality reporting

While modern electronic documentation management systems make accurate recordkeeping, reviewing, updating, and auditing more attainable, proper training and follow-through are still paramount.

Most Common 483s Related to Concurrent Documentation[1]

Biological product deviation report: Failure to submit a biological product deviation report [within 45 days from the date you acquired information suggesting that a reportable event occurred].

Concurrent documentation: Records are not concurrently maintained with the performance of each significant step in the [collection] [processing] [compatibility testing] [storage] [distribution] of each unit of blood and blood components so that all steps can be clearly traced.

5. Combat Concurrent Documentation Issues

Concurrent documentation and product deviation reporting issues are prevalent, specifically in the Biologics category.

Performing tasks and not promptly documenting can lead to a host of data integrity challenges, including misinformation and deviations due to delayed documentation based on memory. These types of dating disparities are certainly not in line with GDP and can land your company in hot water with the FDA.

Often, when an error or deviation is discovered to be missing or incorrect, it is too late to update it accurately. While timely documentation is a one-shot deal that you can improve with adequate training and quality systems, there is one other step you can control to smooth out your process: ensure your team "levels" deviations appropriately.

Categorizing discovered deviations as critical, major, or minor helps your QA team prioritize remediation efforts. Although it can be tempting to categorize every deviation as critical or major, doing so can flood your system and leave your QA team with no real prioritized queue.

Define and document a standard of how to categorize deviations—including concrete examples—then train all staff to identify critical, major, and minor deviations confidently.

With this important distinction, your QA team will be able to accurately assess issue priority, remediate the most impactful deviations first, and avoid any truly critical issues from slipping through the cracks.

Where There is Data, There is Always Room for Improvement

Every sector of the life sciences and pharmaceutical industry can benefit from a thorough evaluation and enhancement of data collection, recording, and review procedures.

As the industry increasingly turns to technology solutions to boost data integrity, the situation will improve—but there is much work that can and should be done before then.

No software now or in the future will offer an immediate solution to pharma's data integrity challenges. Instead of waiting for such a tool, invest now in the personnel, training, and process roadmaps that will make your eventual technology adoption smoother and more impactful with an eye toward 100% right-first-time data entry and streamlined quality review processes.

References

1. Based on data from the FDA Inspectional Observation Data Set for FY 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

2. Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program. https://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019

3. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=820.184

4. Supplier Qualification & Management Guidelines. Active Pharmaceutical Ingredients Committee (APIC). December 2009.

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