



SIX DATA INTEGRITY 483S

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As we continue to follow the data integrity story, let's take a look at six (6) forms 483 associated with data integrity that had broad impact throughout the industry or resulted in serious enforcement actions including consent decree agreements.

You will see that they are not limited to a single country and many of the observations are similar or exactly the same over a decade. The industry has clearly struggled with modifying their practices to ensure compliance. Also, all of these inspection cite observations that are included in the predicate rules, and thus do not represent a change in regulations or interpretation of existing requirements. It's probably impossible to say which are the most 'important' and anyone who has been following this saga probably has their own list of favorites! I've made every effort to choose ones that each represent a different area of focus. These are in no particular order except for the first one.

LET'S GET STARTED:

1) First on my list is the form [483 issued to Able Laboratories located in Cranberry NJ in 2005](#). The firm was a manufacturer of generic drugs. This was not the earliest enforcement action in the area of data integrity, but it did serve to grab the attention of the industry in a way that earlier actions apparently did not.

- It's important to remember that failures in data integrity and data governance is not a problem limited to India and China. The earliest actions, from 1999, were taken against firms in the US.

- FDA provides a painfully detailed tabulation where the company did not investigate or report out of specification results. A collection of false results was submitted in annual reports or other submissions to FDA. Submission of false information to FDA is a criminal act.
- In addition to not addressing OOS results, Analysts and Supervisors substituted passing results for failing results, thus indicating some level of management involvement in the misrepresentation of data.
- The importance of review of electronic data is highlighted in observation #1: *"The Quality Unit failed to: review electronic data as part of batch release, review computer audit trails in the Waters Empower Data Acquisition System and provide adequate training to analytical chemists. These practices led to the Quality Unit releasing batches of drug products which failed to meet in-process, finished product and stability specifications. These practices also led to the submission of erroneous data in Annual Reports and Prior Approval Supplement...The lack of Quality oversight resulted in: the ceasing of manufacturing on 5/13/05 5/19/05, the ceasing of distribution of all drug products on 5/26/05 5/13/05, the recall of all batches (3,184) of drug products and the withdrawal of at least five Abbreviated New Drug Applications."*
- The firm ultimately withdrew over 50 ANDAs and is no longer in business.

2) The eleven-page form [483 issued to the Ranbaxy site in Toansa, India in January 2014](#).

is remarkable because the firm has been under FDA's scrutiny for data integrity deficiencies since at least 2005. Apparently, preventive actions have not had an effect. The firm was placed on the [Application Integrity Policy](#) list. We provide the link to [FDA's letter to Ranbaxy](#) regarding the submission of false information.

The FDA also provides a [summary](#) of all regulatory actions taken against Ranbaxy. Four of Ranbaxy's sites are current under FDA import alerts, the firm entered into a consent decree agreement in 2012, and legal actions resulted in fines of \$500,000. The site associated with this form 483 manufactures APIs.

- The observations are not new, and have been cited before by the agency. The firm is now owned by Sun Pharmaceuticals who have their own challenges in this area.
- The first observation addresses overwriting of original electronic data of failing results and retesting until passing results were obtained. The FDA provides four (4) pages of examples.
- The second observation addresses the practice of pre-injections made before the official sample sequence. This seems to be another example of testing until you get the results that are acceptable.
- Stand-alone computer systems do not have adequate controls to limit access and activities to authorized individuals.
- Records are not completed contemporaneous with their performance. Results were documented on sticky notes or other ways

that were not consistent with documenting results in original records.

3) Eli Lilly and Company, Indianapolis, IN received a 32-page form 483 in

November, 2001 that included observations associated with computer system validation and documentation. I include this one because it's from 2001, fifteen years ago. The investigators were Robert Tollefsen and Thomas Arista, both now national experts in computer systems and aseptic processing respectively. The concepts and observations in recent inspections regarding failure to validate computer systems for their intended purpose are not new. This demonstrates they are at least 15 years old. Note particularly the term 'software life cycle' in the 483, the concept of data and software lifecycle didn't appear just a couple of years ago but has been around for years. This inspection follows on the heels of particularly difficult one in February, 2001. The first 11 pages of this 483 address observations regarding the computer system.

Observations include:

- Failure to have software revision control over the lifecycle and failure to have summary validation reports over the software life-cycle.
- The firm failed to adequately generate approved protocols that identify testing to be performed as part of the change.
- System documentation was inadequate with examples 'a' through 'q', some of which were multi-part.
- Lack of appropriate access control.

- The firm has failed to completely define the network.

The rest of the form 483 addresses problems with laboratory system including sampling and OOS management, media fill simulations, aseptic processing and shortcomings in facilities and equipment.

4) Hill Dermaceuticals in Sanford Florida received a 20-page form 483 in February, 2010 where data integrity deficiencies were identified. They received two warning letters in 2009, [HERE](#) and [HERE](#). Like Ranbaxy, Hill Dermaceuticals is on the [Application Integrity Policy list](#) and entered into a consent decree agreement with the courts in September 2011. We provide the [press release](#) for the agreement. I include this form 483 specifically because of the issue of uncontrolled and rewritten notebooks. Among the observations:

- In 1.e. the QC Manager who had direct responsibility for all QC Operations “manipulated raw data and recreated uncontrolled laboratory notebooks”.
- QC laboratory notebooks are uncontrolled to the point where the firm does not know how many have been issued in the past 5 years.
- The QC Manager rewrote at least three laboratory notebooks between 2005 and 2010 which the QA Manager resigned and backdated.
- Sample weights were invalidated and the final results were changed to passing values.

- The firm lacked accountability for the receipt of samples of raw materials, in-process and finished product.

- HPLC’s do not have equipment logs to identify the lot of materials they were used to test.

5) Formulation Technology Inc. received a form 483 on July 18, 2013. The firm is located in Oakdale, CA. Observations 5,6,7 and 11 are associated with data integrity. It is interesting that none of these observations represent new regulations, requirements or interpretations but rather have been in place for the preceding decade. The observations in question include:

- The computer associated with the gas chromatograph did not require either a user name or a password to log in. Thus, it is not possible to assign actions within the system to a unique individual. Audit trails have not been enabled so it is not possible to determine whether data have been changed or deleted. The GC data are imported to a spreadsheet where the technician can change formulas in the spreadsheet, the formulas have not been validated and the formulas are not reviewed by a second person to make sure they are accurate.
- Laboratory records do not include complete data including identification of the method used, graphs and charts, and a record of all calculations including units of measure and conversion factors where necessary.
- Data are not documented contemporaneous with performance of the activities. Samples of tablets are taken for testing at various times

during manufacture, and transferred to an area outside the tableting room for testing. The results are documented in the batch record, but there is no way to ensure they are accurate because traceability of the tablets samples at the pre-defined internals is not manipulated.

6) Zhejiang Hisun Pharma Co. Ltd is an API manufacturer located in China. They received a 10-page form 483 in March 2015. Their laboratory practice was to delete failing data and test until passing results are obtained. I provide this form 483 because it provides a 6-page listing of the myriad ways in which data were manipulated, including, but not limited to:

- Sample set raw data are deleted, actions are not recorded in the logbook, and all supporting raw data are deleted.
- Trial injection results are deleted from the system.
- Injection results are deleted from the system.

FDA linked this deletion of data to evaluation of customer complaints which is the first time I've seen this linkage.

When the FDA requested to review audit trails for lots that were the subject of customer complaints, it was determined that the firm did not archive meta-data so the audit trails were not available and it could not be established whether the firms test results were valid when compared with customer complaints.



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Barbara serves as FDAzilla’s in-house GMP Quality Expert and is editor-in-chief of GMP Regulatory Intelligence. Most recently, she was the Director of External Quality for Amgen. There, she designed, developed, implemented, and managed a sophisticated and comprehensive GMP Regulatory Intelligence program for 8 years.

A key part of that program was surveillance of the environment on a daily basis and communication of time-sensitive and business-critical information to relevant management and staff in real time. Her newsletter inside Amgen was distributed broadly across the company - from VPs to front-line quality, operations, development and regulatory personnel.

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