



Current Expectations and Guidance Data Integrity

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US FDA Guidance for Industry– April 2016



- ❑ This guidance is a **list of current problems** and how they related to cGMP in 21 CFR 210, and 211
- ❑ It clarifies several terms in FDA regulations
 - ❑ Metadata
 - ❑ Audit trail
 - ❑ Static vs. Dynamic records
 - ❑ Backup
 - ❑ System
- ❑ It is **not** a comprehensive list of data controls or a “how to” guidance

Data Integrity and Compliance With CGMP Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, m. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016

Field Notes

Zooming In on Industry-specific Issues

FDA REGULATION

Maintaining Data Integrity

Avoiding regulator scrutiny in the medical products industry

by Jose Rodriguez Perez

In August 2015, the European Union (EU) banned the marketing of around 700 Indian-made generic drugs for alleged manipulation of clinical trials data. The largest-ever EU-wide suspension of sales and distribution of generic drugs ordered by the European Commission was applicable to all 28 member nations.¹

Recently, there has been a dramatic escalation in the number of U.S. Food and Drug Administration (FDA) warning letters, World Health Organization (WHO) notices of concern, and EU statements of noncompliance in which false or misleading information has been identified during inspections. Failure to properly manage data integrity applies equally to paper and electronic data. It can arise either from poor systematic control of the data management systems due to a lack of knowledge, human error or from intentionally hidden, falsified or misleading data.

What is data integrity?

Data integrity is a global mandatory requirement for the regulated healthcare industry. Developing and bringing a medical product to market involves different players and activities; therefore, robustness and accuracy of the data submitted by manufacturers to regulatory authorities is crucial. The data must be comprehensive, complete, accurate and true to ensure the quality of studies supporting applications for medical products to be placed on the market. Complete, consistent, and accurate data must be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).² See Table 1.

Data integrity also must comply with good manufacturing practices (GMP), good clinical practices (GCP), and good laboratory practices (GLP). In recent years, however, data integrity issues are jeopardizing the regulatory compliance status of organizations. In many instances, data integrity problems are created by sloppy documentation practices or incidents that cause the loss of data, but regulators tend to label those situations as fraud. Moreover, it demonstrates a lack of commitment

chromatography [HPLC] testing sequence versus recording only at the end of the day).

Quality management controls

Data integrity enables good decision-making by manufacturers and regulatory authorities. It is a fundamental mandatory requirement of the medical products quality system, applying equally to manual (paper) and electronic systems. To ensure data integrity, senior management must engage in the promotion of a quality culture along with the implementation of appropriate organizational and technical controls. It requires participation and commitment by staff at all levels within the organization, by the organization's suppliers and by its distributors.

Data integrity is a basic element of good documentation practices, one of the most fundamental pillars of any quality management system, including CGMP. Upper management, and especially quality leaders at every regulated organization must ensure that everyone is accountable for their actions, including having proper documentation of activities performed. Unfortunately, most regulated organizations only react to data integrity issues after regulators discover them.

An outrageous example of this can be found in a warning letter³ issued in July 2014 in which the FDA required an organization to "identify the specific manufacturers in place who participated in, facilitated, encouraged or failed to stop subordinates from falsifying data in CGMP records, and determine the extent of top and middle management's involvement in or awareness of data manipulation." In the same inspection, the FDA also discovered that "your firm falsified documents designed to demonstrate the effectiveness of CGMP

Data integrity is a basic element of good documentation practices, one of the most fundamental pillars of any quality management system, including current good manufacturing practices.

training... That a senior manager was engaged in the falsification of documents is troubling and raises questions about validity of documents generated by your firm."

Senior management, especially those with quality management responsibilities, should ensure that data integrity risk is assessed, mitigated and communicated in accordance with the principles of quality risk management. The effort and resources assigned to data integrity measures should be commensurate with the risk to product quality, and balanced with other QA resource demands. Where long-term measures are identified to achieve the desired state of control, interim measures should be implemented to mitigate risk and should be monitored for effectiveness.

Data integrity and human error

Finally, remember that regulators do not distinguish between human error or sloppiness, and data falsifications and fraud when assessing the impact of data integrity failures, as demonstrated in the following excerpt from a 2015 FDA warning letter.⁴

"In correspondence with the agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to

disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection."⁵

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FOR MORE INFORMATION

Patient/eral Drug Association (PDA). *PDA Letter* April 2015. International Society for Pharmaceutical Engineering. "Special Report: Data Integrity." *Pharmaceutical Engineering*, March/April 2016, Vol. 36, No. 2, pp. 40-66.



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TABLE 1 Complete, consistent and accurate data

Characteristics	Meaning
Attributable	Establishes who performed an action and when. Traceable to an individual.
Legible	Data must be recorded permanently in a durable medium and be readable by others. Traceable changes.
Contemporaneous	Activities must be recorded at the time they occur (when activity is performed or the information is obtained).
Original	The information must be the original record (first capture of the data) or a certified true copy. Not the transcribed data.
Accurate	Data reflect true information.

Field Notes

US FDA Guidance for Industry– April 2016



- ❑ FDA has increasingly observed cGMP violations involving data integrity during cGMP inspections
- ❑ **75%** of warning letters have involved data integrity issues in drug manufacturing since 2015
- ❑ Ensuring data integrity is a critical component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health

What is “data integrity”?

Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)

- **A**tttributable – data are identified with a specific subject and a specific observer and recorder
- **L**egible – data are readable and understandable by humans
- **C**ontemporaneous - data are recorded at the time they are generated or observed
- **O**riginal or true copy– data are recorded for the first time.
- **A**ccurate – data are correct

What is “metadata”?

- ❑ Metadata is the contextual information required to understand data.
- ❑ A data value is by itself meaningless without additional information about the data. Metadata is often described as **data about data**.
- ❑ Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data.
 - ❑ For example, the number “23” is meaningless without metadata, such as the unit “mg”
 - ❑ Among other things, metadata for a particular piece of data could include a date/time stamp for when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, audit trails, etc.
- ❑ Data should be maintained throughout the record’s retention period with all associated metadata required to reconstruct the cGMP activity (§ 211.188 and § 211.194). The relationships between data and their metadata should be preserved in a secure and traceable way₆

What is an “audit trail”?

- ❑ *Audit trail* means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record.
- ❑ An audit trail is a chronology of the “who, what, when, and why” of a record.
 - ❑ For example, the audit trail for a HPLC run could include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any, including change justification for the reprocessing.
- ❑ Electronic audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).

Static vs. dynamic records

- ❑ *Static* is used to indicate a fixed-data document such as a **paper record** or an **electronic image**,
- ❑ *Dynamic* means that the record format allows interaction between the user and the record content.
 - ❑ For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger.
 - ❑ It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as calculated yield.

Backup



- ❑ FDA uses the term *backup* in § 211.68(b) to refer to a **true copy of the original data that is maintained securely throughout the records retention period** (§ 211.180).
- ❑ The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format.
- ❑ This should not be confused with backup copies that may be created during normal computer use and temporarily maintained for disaster recovery (e.g., in case of a computer crash or other interruption). Such temporary backup copies would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

What are the “systems” in “computer or related systems” in § 211.68?



- ❑ The American National Standards Institute (ANSI) defines *systems* as people, machines, and methods organized to accomplish a set of specific functions.
- ❑ *Computer or related systems* can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

Attributable



PAPER

- ❑ Initials
 - ❑ CGS
- ❑ Manuscript signature
 - ❑ *Carmen Gómez Sánchez*

ELECTRONIC

- ❑ Log-on User ID
 - ❑ cgomez
- ❑ Electronic signature
 - Author: Carmen Gómez,
 - 09JAN2016 09:12:54
 - GMT

Legible



PAPER

- Only permanent ink
- Black or blue ink
- Never use correction liquid
- No pencil
- Date and properly initial written corrections

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- Automatic saving
- Do not over-writing
- Do not delete information
- Hidden fields must be visible
- Audit trail captures any change
- Security copies and archiving

Contemporaneous (concurrent)



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- ❑ NO back-dating
- ❑ GMP activities must be *documented at the time of performance*
- ❑ Date/time is documented (if applicable)

ELECTRONIC

- ❑ *Data is Automatically saved after Input*
- ❑ Automatic saving and synchronization of date/time

Original

- ❑ Data transcription is **not allowed**
 - No scratch paper, no post-it notes
 - Data are recorded **for the first time directly** into the official register
 - Certified copies: true copies of an original document



Accurate

- ❑ **Data are correct** (*Calculations, algorithms, analyses, etc*)
- ❑ Data accuracy is based on several elements of our quality system such as:
 - Equipment qualification, calibration and maintenance
 - Computer system validation
 - Internal quality audits and self-inspections
 - Good documentation practices

Paper requirements = electronic requirements



The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the **same** requirements

Data Integrity: Not a New Concept

Principles from the paper-and-ink era **still** apply:

- ❑ §211.68 requires that backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss
- ❑ §212.110(b) requires that data be stored to prevent deterioration or loss
- ❑ §§211.100 and 211.160 require that certain activities be documented at the time of performance and that laboratory controls be scientifically sound
- ❑ §211.180 requires true copies or other accurate reproductions of the original records; and
- ❑ §§211.188, 211.194, and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

Data Integrity: Not a New Concept

API-ICH Q7 Rev 1



Computerized Systems (5.4)

- ❑ GMP-related computerized systems should be validated.
- ❑ Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- ❑ Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
- ❑ Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

When is it permissible to exclude cGMP data from decision making?



- ❑ Any data created as part of a cGMP record must be evaluated by the quality unit as part of release criteria (§ 211.22 and § 212.70) and maintained for cGMP purposes (§ 211.180).
- ❑ Electronic data generated to fulfill cGMP requirements should include relevant metadata.
- ❑ To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion (see the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, and § 211.188, § 211.192, and §212.71(b)).

Does each workflow on our computer system need to be validated?



- ❑ **Yes**, a workflow, such as creation of an electronic master production and control record (MPCR), is **an intended use** of a computer system to be checked through validation (see § 211.63, § 211.68(b), and § 211.110(a)).
- ❑ If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly.
 - ❑ For example, qualifying the Manufacturing Execution System (MES) platform, a computer system, ensures that it meets specifications; however, it does not demonstrate that a given MPCR generated by the MES contains the correct calculations.
 - ❑ In this example, **validating the workflow** ensures that the intended steps, specifications, and calculations in the MPCR are accurate.

Does each workflow on our computer system need to be validated? cont.



- ❑ This is similar to reviewing a paper MPCR and ensuring all supporting procedures are in place before the MPCR is implemented in production (see § 211.100 and § 211.186).
- ❑ FDA recommends you implement appropriate controls to manage risks associated with each element of the system. Controls that are appropriately designed to validate a system for its intended use address
 - ❑ software,
 - ❑ Hardware
 - ❑ Personnel
 - ❑ documentation.

How should access to cGMP computer systems be restricted?



- ❑ FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data).
- ❑ FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel **independent** from those responsible for the record content.
- ❑ FDA recommends maintaining a list of authorized individuals and their access privileges for **each** cGMP computer system in use

Why is FDA concerned with the use of shared login accounts for computer systems?



- ❑ “...you must implement documentation controls that ensure actions are attributable to a specific individual.”
- ❑ When login credentials are shared, a unique individual cannot be identified
- ❑ On paper you would sign/initial and date your work or the review of other’s work

How should blank forms be controlled?



- ❑ There must be document controls in place to assure product quality (§ 211.100, § 211.160(a), § 211.186).
- ❑ FDA recommends that, if used, blank forms (including, but not limited to, worksheets, laboratory notebooks, and MPCRs) **be controlled** by the quality unit or by another document control method. For example, numbered sets of blank forms may be issued as appropriate and should be reconciled upon completion of all issued forms. Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement (§ 211.192, § 211.194).
- ❑ Similarly, **bound paginated** notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages.

How often should audit trail be reviewed?



- ❑ FDA recommends that audit trails that capture changes to **critical data** be reviewed with each record and before final approval of the record
- ❑ Audit trails subject to regular review should include changes to: history of finished product test results, sample run sequences, sample identification, critical process parameters
- ❑ FDA recommends routine scheduled audit trail review based in the complexity and the intended use of the system

Who should review audit trails?

- ❑ **Audit trails are considered part of the associated records.**
- ❑ Personnel responsible for record review under cGMP should review the audit trails that capture changes to critical data associated with the record as they review the rest of the record (§ 211.22(a), § 211.101(c), § 211.194(a)(8)).
 - ❑ For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit (§ 211.192).
 - ❑ This is similar to the expectation that cross-outs on paper be assessed when reviewing data.

Can electronic copies be used as accurate reproductions of paper or electronic records?



- ❑ **Yes.** Electronic copies can be used as true copies of paper or electronic records, provided the copies **preserve** the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records.
- ❑ True copies of dynamic electronic records may be made and maintained in the format of the original records or in a compatible format, provided that the content and meaning of the original records are preserved and that a suitable reader and copying equipment (for example, software and hardware, including media readers) are readily available (§ 211.180(d)).

Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?



- ❑ A paper printout or static record may satisfy retention requirements if it is a complete copy of the original record (see § 211.68(b), § 211.188, and § 211.194).
- ❑ For example, pH meters and balances may create a paper printout or static image during data acquisition as the original record. In this case, the paper printout or static image created during acquisition, or a true copy, should be retained (§ 211.180).

Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument? cont.



- ❑ However, electronic records from certain types of laboratory instruments are **dynamic** records, and a printout or a static record **does not preserve** the dynamic format which is part of the complete original record.
- ❑ For example, the spectral file created by FT-IR (Fourier transform infrared spectroscopy) can be reprocessed, but a static record or printout is fixed, which would not satisfy cGMP requirements to retain original records or true copies (§ 211.180(d)).
 - ❑ Also, if the full spectrum is not displayed, contaminants may be excluded.
- ❑ Control strategies must ensure that original laboratory records, including paper and electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain that all test results are appropriately reported.

Can electronic signatures be used instead of handwritten signatures for master production and control records?



- ❑ **Yes**, electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any cGMP required record.
- ❑ While § 211.186(a) specifies a “full signature, handwritten,” part of the intent of the full signature requirement is to be able to clearly identify the individual responsible for signing the record.
- ❑ An electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement
 - ❑ 21 CFR 11 establishes criteria for when electronic signatures are considered the legally binding equivalent of handwritten signatures
- ❑ Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.

When does electronic data become a cGMP record?



- ❑ When generated to satisfy a cGMP requirement, **all data** become a cGMP record
- ❑ You must document, or save, the data at the time of performance to create a record
- ❑ FDA expects processes to be designed so that quality data required to be created and maintained cannot be modified. For example, chromatograms should be sent to long-term storage (archiving or a permanent record) upon run completion instead of at the end of a day's runs.

When does electronic data become a cGMP record? cont.



- ❑ It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook (§ 211.100(b), § 211.160(a), and § 315 211.180(d)).
- ❑ Similarly, it is not acceptable to store data electronically in temporary memory, in a manner that allows for manipulation, before creating a permanent record.
- ❑ Electronic data that are automatically saved into temporary memory do not meet cGMP documentation or retention requirements.

When does electronic data become a cGMP record? cont.



- ❑ You may employ a combination of technical and procedural controls to meet cGMP documentation practices for electronic systems. For example, a computer system, such as a Laboratory Information Management System (LIMS) or an Electronic Batch Record (EBR) system, can be designed to automatically save **after each separate entry**.
- ❑ This would be similar to recording each entry contemporaneously on a paper batch record to satisfy cGMP requirements. The computer system could be combined with a procedure requiring data be entered immediately when generated.

What is wrong with using samples during system suitability or test, prep, or equilibration runs?

- ❑ FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result
 - ❑ Testing different samples until the desired passing result is obtained). This practice, also referred to as *testing into compliance*, is not consistent with cGMP
 - ❑ In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance.
- ❑ We would consider it a **violative practice** to use an actual sample in *test, prep, or equilibration* runs as a means of disguising testing into compliance.

What is wrong with using samples during system suitability or test, prep, or equilibration runs? cont

- ❑ According to the USP, system suitability tests should include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied
- ❑ System suitability tests, including the identity of the preparation to be injected and the rationale for its selection, should be performed according to the firm's written procedures and the approved application or applicable compendial monograph (§ 211.160).

What is wrong with using samples during system suitability or test, prep, or equilibration runs? cont

If an actual sample is to be used for system suitability testing, it should be:

- ❑ a properly characterized **secondary standard**,
- ❑ written procedures should be established and followed,
- ❑ **and** the sample should be from a **different batch** than the sample(s) being tested (§ 211.160, and § 211.165).
- ❑ All data should be included in the record that is retained and subject to review **unless** there is documented scientific justification for its exclusion.

Is it acceptable to only save the final results from reprocessed laboratory chromatography?



- ❑ **No.** Analytical methods should be capable and stable
- ❑ For most lab analyses, reprocessing data should not be regularly needed. If chromatography is reprocessed, written procedures must be established and followed and **each result retained for review** (§ 211.160(a), § 211.160(b), § 211.165(c), and § 211.194(a)(4))
- ❑ FDA requires complete data in laboratory records, which includes raw data, graphs, charts, and spectra from laboratory instruments (§ 211.194(a))

Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented cGMP quality system?



- ❑ **No.** Suspected or known falsification or alteration of records required under parts 210 and 211 must be fully investigated under the cGMP quality system to
 - ❑ determine the effect of the event on patient safety, product quality, and data reliability;
 - ❑ to determine the root cause; and
 - ❑ to ensure the necessary corrective actions are taken (§ 211.22(a), § 211.125(c), § 211.192, § 211.198, and § 211.204)

- ❑ *FDA invites individuals to report suspected data integrity issues at DrugInfo@fda.hhs.gov. “cGMP data integrity” should be included in the subject line of the email.*

Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?

- ❑ **Yes.**
- ❑ Training personnel to detect data integrity issues is consistent with the personnel requirements under § 211.25, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

Is the FDA investigator allowed to look at my electronic records?



- ❑ **Yes.**
- ❑ All records required under cGMP are subject to FDA inspection. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§ 211.180(c)).

How does FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?



FDA encourages you to demonstrate that you have effectively remedied your problems by:

- ❑ hiring a third party auditor
- ❑ determining the scope of the problem
- ❑ implementing a **global** corrective action plan
- ❑ **removing at all levels individuals responsible for problems from cGMP positions.**
- ❑ FDA may conduct an inspection to decide whether cGMP violations involving data integrity have been remedied

Last Words: If You Find a Data Integrity Problem...



- ❑ Determine scope, severity, and risks
- ❑ Disclose *
- ❑ Commit to voluntary remediation

* FDA is much more willing to work with firms that voluntarily disclose and commit to fixing and preventing problems.

Clear Accountability for Data Integrity

- ❑ Consider implementing an enhanced ethics program focused on data integrity awareness
- ❑ Data integrity problems are not always intentional: sometimes they result from poorly controlled systems
 - ❑ In correspondence with the agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection.” Warning Letter January 2015

A Tale of Two Firms

Firm 1: DI event transpires (bonus: reported through company hotline!).

- ❑ Investigation, CAPA, and assessment of effects on product quality/risks to patients are well defined and understood. Self-audit and CAPA. FDA learns about the events and CAPAs during a scheduled inspection.

Firm 2: Adverse event triggers FDA inspection. During inspection of the lab, we observe:

- ❑ Results have been deleted or replaced; some results not recorded or reported as part of complete records.
- ❑ Many analyses were performed without use of audit trails; many analysts shared passwords and permissions.
- ❑ 483 Response: This is an isolated event! We will retest the relevant lots and fire the people responsible!

Warning Letter Response

Data Integrity Requirements



- 1) Identify any historical period(s) during which inaccurate data reporting occurred at your facilities.
- 2) Identify and interview your current employees who were employed prior to, during, or immediately after the relevant period(s) to identify activities, systems, procedures, and management behaviors that may have resulted in or contributed to inaccurate data reporting.
- 3) Identify former employees who departed prior to, during, or after the relevant periods and make diligent efforts to interview them to determine whether they possess any relevant information regarding any inaccurate data reporting.
- 4) Determine whether other evidence supports the information gathered during the interviews, and determine whether additional facilities were involved in or affected by inaccurate data reporting.

Warning Letter Response

Data Integrity Requirements



- 5) Use organizational charts and SOPs to identify the specific managers in place when the inaccurate data reporting was occurring and determine the **extent of top and middle management involvement in, or awareness of, data manipulation.**

- 6) Determine whether any individual managers identified in item (5) above are still in a position to influence data integrity with respect to CGMP requirements or the submission of applications; and establish procedures to expand your internal review to any other facilities determined to be involved in, or affected by, the inaccurate data reporting.

Warning Letter 2016



- ❑ During the inspection, FDA's investigator discovered a lack of basic laboratory controls to prevent changes to and deletions from your firm's electronically-stored data. Your firm relied on incomplete and falsified records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.
- ❑ Our investigator found that your firm failed to prevent data manipulation on multiple computerized analytical systems. Your firm re-tested samples without justification and deleted raw analytical data from computerized systems.

Warning Letter 2016 cont.

- ❑ For example, on March 4, 2016, your analyst set the GC personal computer (PC) clock back to make it appear as if testing had been done **seven months earlier** – on August 3, 2015. The analyst then performed five different injections to produce falsified results for long term stability 25C/65% RH 12 month time-point residual solvent testing for finished API lot **(b)(4)**. The analyst deleted the first four backdated results and reported only the results of the fifth and final injection as passing in the quality control data package.
- ❑ When our investigator asked your staff about these instances of falsification and manipulation, your quality control manager stated that your firm “**forgot**” to perform stability testing and therefore created falsified results for each missed time point by manipulating the controlling PC clock.

Warning Letter 2013



We observed and documented practices during the inspection that kept some samples, data and results outside of the local systems for assessing quality. **This raises serious concerns regarding the integrity and reliability of the data generated at your plant.** For example,

- a) Our review of the Chromeleon and Empower II software found that your firm was testing samples unofficially, and not reporting all results obtained. Specifically, “test,” “trial” and “demo” injections of API samples were performed, **prior** to performing the tests that would be reported as the final QC results.
- b) Out-of-specification or undesirable results were ignored and not investigated.
- c) Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APIs intended for US distribution.
- d) Unacceptable practices in the management of electronic data were also noted. The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted.

Warning Letter 2013



- ❑ You have also recently informed us that HPLC units and PCs were removed from the facility for the duration of the inspection to conceal data manipulations. This action, which apparently also occurred in association with past inspections, is very worrisome to us and should be explained in your response to this letter.
- ❑ An employee was observed attempting to hide manufacturing related records in his pocket from the FDA Investigator.
- ❑ During the inspection your firm also repeatedly delayed, denied, limited or refused to provide information to the FDA investigators. Please be reminded that the Food and Drug Administration Safety and Innovation Act (FDASIA) § 707, also deems a product to be adulterated if drugs have been manufactured, processed, packed or held in an establishment by an owner or operator who has delayed, denied, or **limited** an inspection.
- ❑ During the inspection, foreign material was observed inside the room 103. A request to open the room was made by the Investigator, which was delayed until a knowledgeable person became available. Upon returning to the area, the room had been cleaned. The FDA was informed that no material was present and that what appeared to be foreign material was **a reflection of the light**. However, the next day a deviation report was prepared documenting the presence of the foreign material and the written instruction to clean the equipment.

Warning Letter 2014



- ❑ Your firm’s response to the Form FDA-483 acknowledges the deficiencies regarding data integrity observed during this inspection. Nevertheless, your firm’s health hazard evaluation “Drug Safety Analysis” conducted in response to the Form FDA-483 concluded that there **was no effect on product quality** or patient safety. However, this evaluation was **based on unreliable and incomplete data**, as undesired records appear to be excluded.
- ❑ Failure to record activities at the time they are performed.
 - ❑ Specifically, your staff used “finished product reports review data” worksheets to document critical laboratory information days after the actual testing was performed.
- ❑ ... we remain concerned about the **capability** and **credibility** of your quality control laboratory.

Warning Letter 2014



- ❑ Our inspection revealed “unofficial” visual inspection records, signed by production personnel, with data that is different from the official batch records reviewed by your firm’s quality unit.
- ❑ In many of the cases reviewed, the unofficial records showed significantly more quality defects than the official batch records. For example, for one lot of injectable product, the unofficial record completed by production personnel showed 200 units failing to meet specifications. Production personnel later completed the official batch record for this batch, showing only 18 units as having been rejected.
- ❑ During the inspection, your firm was unable to demonstrate that all units with quality defects were in fact rejected.

Warning Letter 2014

- ❑ The use of unofficial and scratch paper records is not acceptable cGMP. The inspection revealed your firm's use of scratch paper containing critical manufacturing data. The data on these scratch paper records did not always match the data on the corresponding official batch records, as in the case for the amount of raw materials added to (b)(4) Suspension USP (b)(4)% Batch (b)(4). Although your firm stated that this batch was destroyed on October 18, 2013, the investigators observed that your records showed that the batch was removed from quarantine on October 25, 2013.
- ❑ The inspection revealed that your firm **falsified** documents designed to demonstrate the effectiveness of cGMP training. Your production head admitted to pre-filling out the answers to post-training comprehension assessment questions and entering the names of employees on these documents. Your company policies require personnel to demonstrate understanding of training through evaluation.

Warning Letter 2015



Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data. Your firm did not have proper controls in place to prevent the unauthorized manipulation of your electronic raw data. For example,

- a) The inspection found that the audit trail feature for your gas chromatography (GC) instruments was not used until October 2013, even though your 2009 GC software validation included a satisfactory evaluation of the audit trail capability.
- b) There is no assurance that you maintain complete electronic raw data for the GC instruments, the Malvern particle size analyzer, and the ultraviolet (UV) spectrophotometer. Our inspection found that these instruments were connected to stand-alone computers that stored the data and that the data could be deleted.

Warning Letter 2013



Your firm repeatedly delayed, denied, limited an inspection or refused to permit the FDA inspection. Examples are as follows:

- ❑ a. On March 18, 2013, an FDA investigator identified the presence of torn raw data records in the waste area and asked one of your firm's QA Officers to remove these torn raw data records for the investigator's review. This QA Officer presented the FDA investigator with approximately 20 paper records, **none of which included raw data entries identified in the waste area earlier** during the inspection.
- ❑ The FDA investigator asked **three times** if there were any more records found in the waste area, and the QA Officer responded to each question, "no, this is all of the records". The FDA investigator then re-visited the waste area and found that the raw data records had been removed and placed in a different holding bag. These records included: raw data testing from anti-microbial effectiveness studies, controlled Master Batch Records, equipment calibration records, and stability protocol records.

Warning Letter 2013

- ❑ On March 19, 2013, an FDA investigator interviewed the Production Head regarding his knowledge of the **unofficial batch record forms being used to record the results for the visual inspection of drug products**. The Production Head stated that he had only seen this unofficial defect data for "1 to 2 batches". The FDA investigator had an earlier conversation with two manufacturing operators, who stated that the Production Head had directed this practice throughout the manufacturing facility and regularly requested and reviewed the unofficial BMR visual inspection results. On March 21, 2013, the Production Head stated that he was fully aware of the practice of using unofficial batch record copies during the course of manufacturing operations.
- ❑ The Production Head acknowledged that **he had provided inaccurate information** in the previous instances.

Warning Letter 2015



Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b)).

- ❑ You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters.
- ❑ Access to production equipment used in parenteral manufacturing and solid dosage forms used a **password shared by four or five individuals** to gain access to each individual piece of equipment and access level. During our inspection, your Executive Production and QA manager confirmed that the password was shared. Neither your operators nor your supervisors had individual passwords.

Warning Letter 2013



Failure to follow and document quality-related activities at the time they are performed.

- ❑ During this inspection, your QC Chemist admitted that, under the direction of a senior colleague, he had recorded false visual examination data in the logbooks for reserve samples. This QC Chemist was responsible for multiple entries in logbooks. Your firm's failure to prevent, detect, and rectify the falsification of your GMP documentation is concerning. In response to this letter, describe your investigation into this misconduct and clearly explain how you determined the extent of the data falsification. Describe the role of the senior colleague who advised the QC Chemist during this incident.

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