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Data Integrity

Investigation &
How to Identify Root Cause

Udaykumar K. Rakibe
M.Pharm.Ph.D., M.B.A.

Andheri (W), Mumbai, Maharashtra, India, 400053.
+91 7756848484 | Pharmantra.expert@gmail.com

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Purpose

To describe the Data and Data Integrity in Quality and Manufacturing records . Describe the process for **investigation and analysis** of any failure, incident or discrepancy in order to identify the root cause/ probable cause.

Integrating quality control into ongoing production process **to catch problems as soon as they occur**.

To provide a **brief description of investigation methods and documentation** to assist the investigation team.

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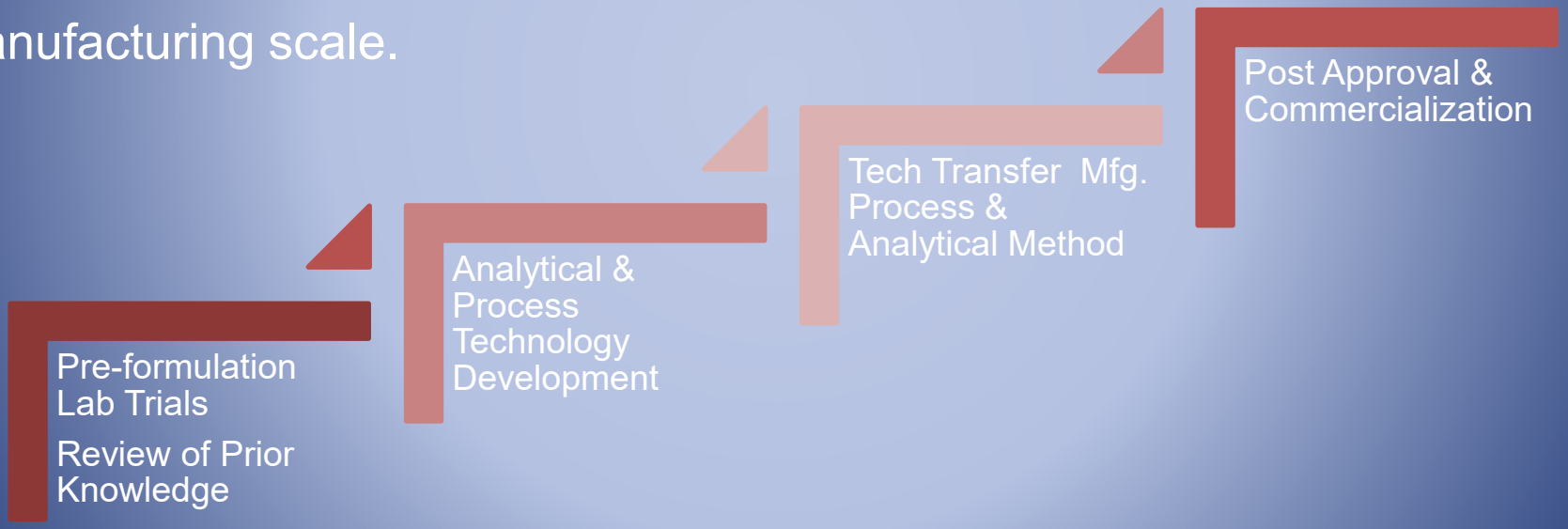
Purpose

To describe the importance and **need and involvement in Data management and maintaining Data Integrity. The process to** initiate the Investigations of Root cause - Pharmaceutical Development, Manufacturing scale-up, scale-up challenges/process validation/failure mitigation at manufacturing scale.



Scope

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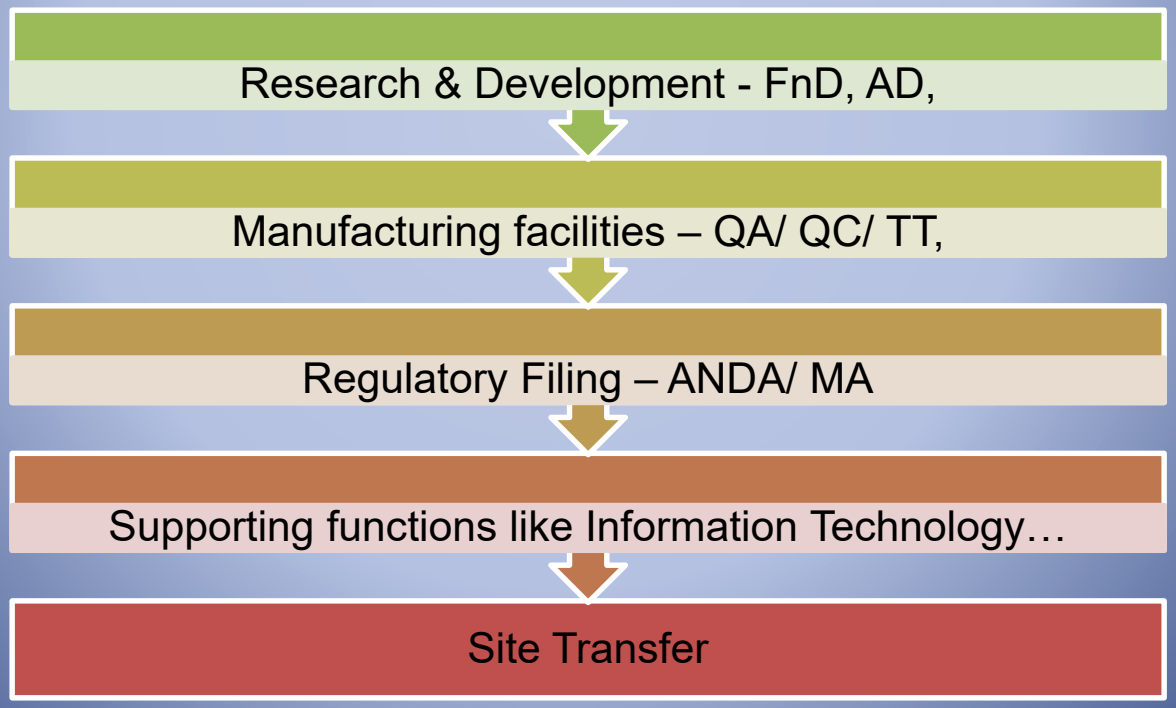
Applicable to **all the data involved in manufacturing and testing at manufacturing site. Involves all the activities and investigations** conducted at manufacturing facilities, and supporting functions like Information Technology…

Applicable to Development, Scaling-up the manufacturing & analytical process/ methods - Bio-batch and commercial batches; including all the post scale-up changes, investigations conducted at –



Data Integrity Importance

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- Breaches conceal patient risk
- Data integrity breach breaks confidence between regulator and regulated
- FDA “relies on firms to do the right thing when [it is] not there”
- Enhances and sustains brand
- Provides basis for management oversight of systems and processes
- Without reliable and accurate data, building efficient and robust systems is difficult or impossible
- Reduced risk of enforcement action
- Competitive advantage for firms

Data Integrity Importance

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Requirement that data are complete, consistent, and accurate “ALCOA”

- ✓ Attributable –e-signature
- ✓ Legible –no overwriting
- ✓ Contemporaneous –time stamp
- ✓ Original/true copy –audit trail
- ✓ Accurate -validation

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211.100, 211.160: certain activities must be documented at the time of performance and laboratory controls must be sound

211.68: backup data must be secure and complete and secure from alteration, erasures, and loss

211.80: requires true copies or other accurate reproductions of the original records

211.188, 211.194, 212.60(g): require complete information, complete data derived from tests, complete records of all tests performed.

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

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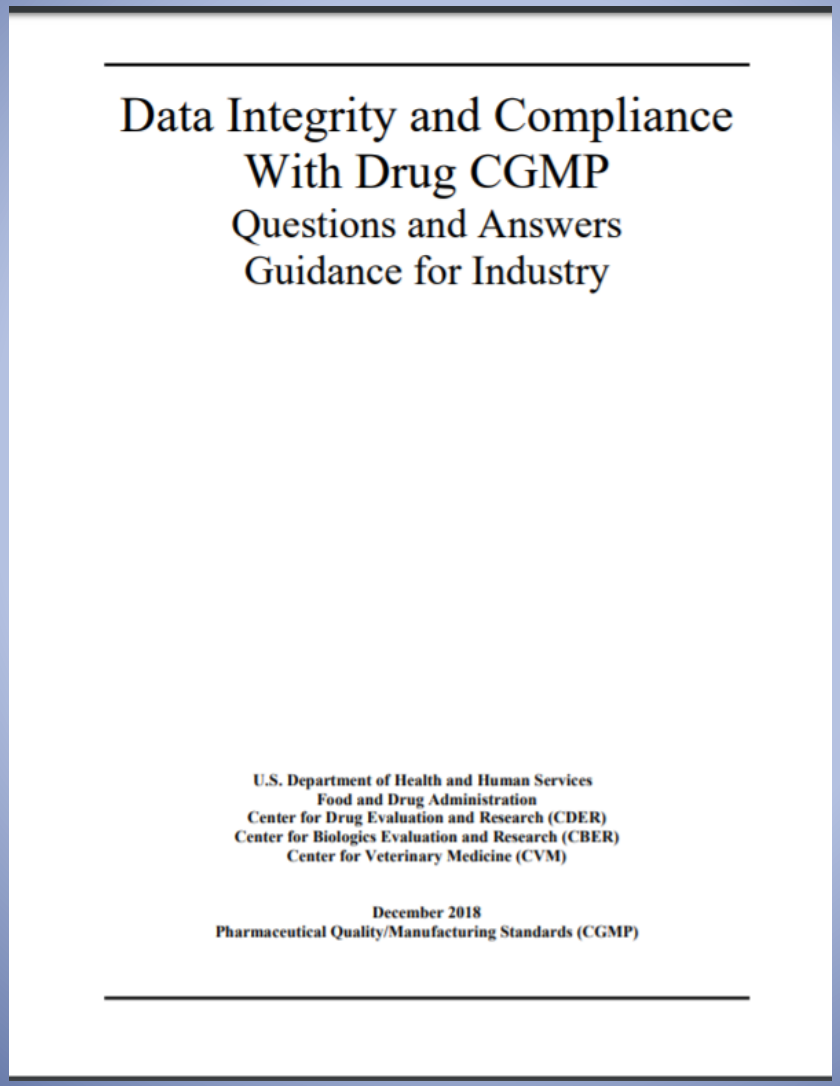

Data Integrity and Compliance
With Drug CGMP
Questions and Answers
Guidance for Industry

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)

December 2018
Pharmaceutical Quality/Manufacturing Standards (CGMP)

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Contains Nonbinding Recommendations

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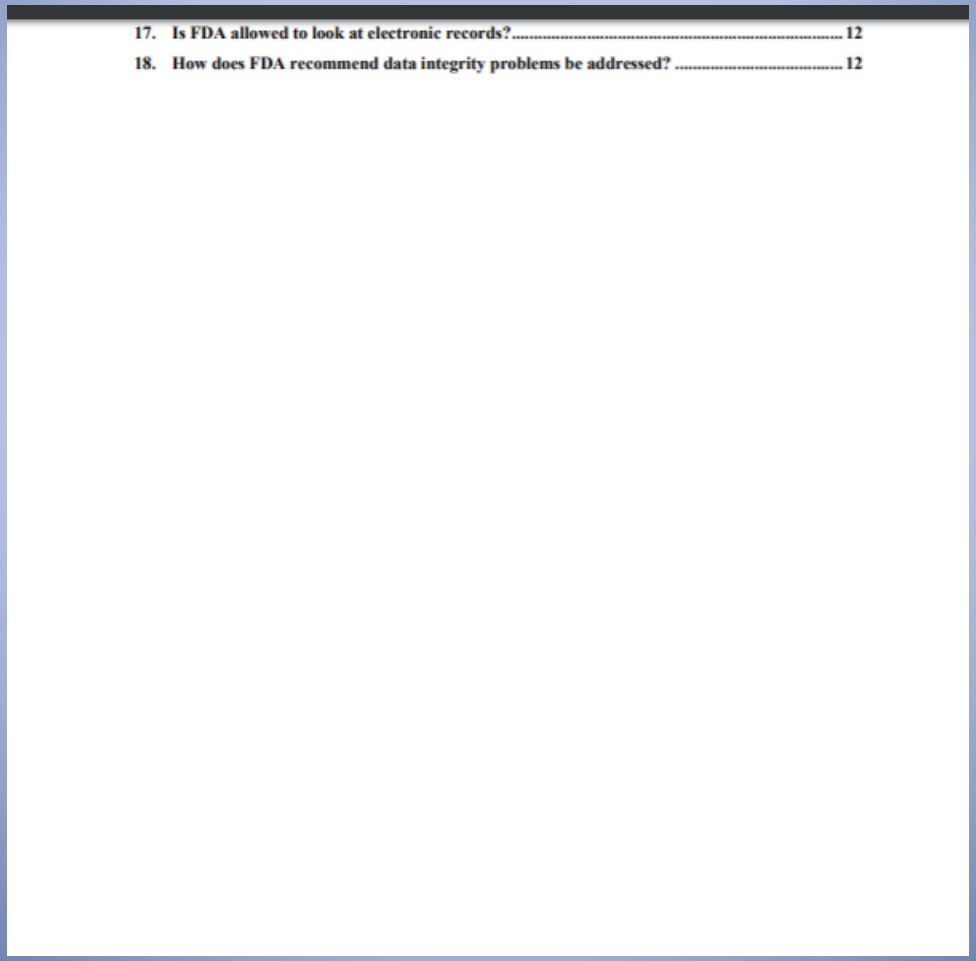

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FDA expects that all data be ***reliable and accurate*** (see the "Background" section).

- CGMP regulations and guidance allow for flexible and risk-based strategies to ***prevent and detect*** data integrity issues.
- Firms should ***implement*** meaningful and effective strategies to manage their data integrity risks based on their process understanding and knowledge management of technologies and business models.
- Meaningful and effective strategies should consider the design, operation, and monitoring of systems and controls ***based on risk to patient, process, and product.***
- ***Management's involvement*** in and influence on these strategies is essential in preventing and correcting conditions that can lead to data integrity problems.
- It is the role of management with executive responsibility to ***create a quality culture where employees understand that data integrity*** is an organizational core value and employees are encouraged to identify and promptly report data integrity issues.
- ***In the absence of management support*** of a quality culture, quality systems can break down and lead to ***CGMP noncompliance***.

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In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health.

These data integrity-related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts, and consent decrees. The underlying premise in §§ 210.1 and 212.2 is that CGMP sets forth minimum requirements to assure that drugs meet the standards of the FD&C Act regarding safety, identity, strength, quality, and purity.

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Requirements with respect to data integrity in parts 211 and 212 include, among other things:

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

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Requirements with respect to data integrity in parts 211 and 212 include, among other things:

- §§ 211.22, 211.192, and 211.194(a) (requiring that production and control records be “reviewed” and that laboratory records be “reviewed for accuracy, completeness, and compliance with established standards”).
- §§ 211.182, 211.186(a), 211.188(b)(11), and 211.194(a)(8) (requiring that records be “checked,” “verified,” or “reviewed”).hings:

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a. What is "data integrity"?

For the purposes of this guidance, 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). Data integrity is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record's retention period ends. System design and controls should enable easy detection of errors, omissions, and aberrant results throughout the data's life cycle.

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b. ***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 an indication of the unit "mg." Among other things, metadata for a particular piece of data could include a date/time stamp documenting 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, material status data, the material identification number, and audit trails. Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194). The relationships between data and their metadata should be preserved in a secure and traceable manner.

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c. ***What is an "audit trail"?***

For purposes of this guidance, 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. For example, the audit trail for a high performance liquid chromatography (HPLC) run should include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any. Documentation should include change justification for the reprocessing.

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). CGMP-compliant record-keeping practices prevent data from being lost or obscured and ensure that activities are documented at the time of performance (see §§ 211.68, 211.100, 211.160(a), 211.188, and 211.194). Electronic record-keeping systems, which include audit trails, can support these CGMP requirements.

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d. ***How does FDA use the terms "static" and "dynamic" as they relate to record formats?***

For the purposes of this guidance, static is used to indicate a fixed-data record such as a paper record or an electronic image, and 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.

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e. ***How does FDA use the term "backup" in § 211.68(b)?***

FDA uses the term backup in § 211.68(b) to refer to a true copy of the original record that is maintained securely throughout the record retention period (e.g., § 211.180). Backup data must be exact, complete, and secure from alteration, inadvertent erasures, or loss (§ 211.68(b)). 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. FDA's use of the term backup is consistent with the term archive as used in guidance for industry and FDA staff General Principles of Software Validation. Temporary backup copies (e.g., in case of a computer crash or other interruption) would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

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f. ***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, personnel, and associated documents (e.g., user manuals and standard operating procedures).

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When is it permissible to invalidate a CGMP result and exclude it from the determination of batch conformance?

Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180).9 Electronic data generated to fulfill CGMP requirements include relevant metadata required to reconstruct the CGMP activity captured in the record. Invalidating test results to exclude them from quality unit decisions about conformance to a specification requires a valid, documented, scientifically sound justification. See, for example, §§ 211.160(b), 211.188, 211.192, and 212.71(b) and the guidance for industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production. Even if test results are legitimately invalidated on the basis of a scientifically sound investigation, the full CGMP batch record provided to the quality unit would include the original (invalidated) data, along with the investigation report that justifies invalidating the result. 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.

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How should access to CGMP computer systems be restricted?

You must exercise appropriate controls to assure that changes to computerized MPCRs or other CGMP records or input of laboratory data into computerized records can be made only by authorized personnel (§ 211.68(b)). Other examples of records for which control should be restricted to authorized personnel include automated visual inspection records, electronic materials management system records, and automated dispensing system weighing records. FDA recommends that you restrict the ability to alter specifications, process parameters, data, or manufacturing or testing methods by technical means where possible (e.g., by limiting permissions to change settings or data). The system administrator role, including any rights to alter files and settings, should be assigned to personnel independent from those responsible for the record content. To assist in controlling access, it is important that manufacturers establish and implement a method for documenting authorized personnel's access privileges for each CGMP computer system in use (e.g., by maintaining a list of authorized individuals) (see § 211.68(b)).

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

When login credentials are shared, a unique individual cannot be identified through the login and the system would not conform to the CGMP requirements in parts 211 and 212. FDA requires that system controls, including documentation controls, be designed in accordance with CGMP to assure product quality (e.g., §§ 211.100 and 212.50). For example, you must implement documentation controls that ensure that the actions as described in question 4 are attributable to a specific individual (see §§ 211.68(b), 211.188(b)(11), 211.194(a)(7) and (8), and 212.50(c)(10)). Shared, read-only user accounts that do not allow the user to modify data or settings are acceptable for viewing data, but they do not conform with the part 211 and 212 requirements for actions, such as second person review, to be attributable to a specific individual.

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How should blank forms be controlled?

There must be document controls in place to assure product quality (see §§ 211.100, 211.160(a), 211.186, 212.20(d), and 212.60(g)). For example, bound paginated notebooks, stamped for official use by a document control group, provide good document control because they allow easy detection of unofficial notebooks as well as any gaps in notebook pages. If used, blank forms (e.g., electronic worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method. As appropriate, numbered sets of blank forms may be issued 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 (see, e.g., §§ 211.192, 211.194, 212.50(a), and 212.70(f)(1)(vi)). All data required to recreate a CGMP activity should be maintained as part of the complete record.

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Who should review audit trails?

Audit trail review is similar to assessing cross-outs on paper when reviewing data. Personnel responsible for record review under CGMP should review the audit trails that capture changes to data associated with the record as they review the rest of the record (e.g., §§ 211.22(a), 211.101(c) and (d), 211.103, 211.182, 211.186(a), 211.192, 211.194(a)(8), and 212.20(d)). For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit (§ 211.192). The regulations provide flexibility to have some activities reviewed by a person directly supervising or checking information (e.g., § 211.188). FDA recommends a quality system approach to implementing oversight and review of CGMP records.

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How often should audit trails be reviewed?

If the review frequency for the data is specified in CGMP regulations, adhere to that frequency for the audit trail review. For example, § 211.188(b) requires review after each significant step in manufacture, processing, packing, or holding, and § 211.22 requires data review before batch release. In these cases, you would apply the same review frequency for the audit trail. If the review frequency for the data is not specified in CGMP regulations, you should determine the review frequency for the audit trail using knowledge of your processes and risk assessment tools. The risk assessment should include evaluation of data criticality, control mechanisms, and impact on product quality.13 Your approach to audit trail review and the frequency with which you conduct it should ensure that CGMP requirements are met, appropriate controls are implemented, and the reliability of the review is proven. See the audit trail definition in 1.c. above for further information on audit trails

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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 record, which includes all metadata required to reconstruct the CGMP activity 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 format that allows for the content and meaning of the original records to be preserved if a suitable reader and copying equipment (e.g., software and hardware, including media readers) are readily available (§§ 211.180(d) and 212.110).

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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 the original record or a true copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). During data acquisition, for example, pH meters and balances may create a paper printout or static record as the original record. In this case, the paper printout or static record, or a true copy, must be retained (§ 211.180). However, electronic records from certain types of laboratory instruments—whether stand-alone or networked—are dynamic, and a printout or a static record does not preserve the dynamic record format that is part of the complete original record. For example, the spectral file created by FT-IR (Fourier transform infrared spectroscopy) is dynamic and can be reprocessed. However, a static record or printout is fixed and would not satisfy CGMP requirements to retain original records or true copies (§ 211.180(d)).

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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?

Also, if the full spectrum is not displayed in the printout, contaminants may be excluded. You 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 and associated information are appropriately reported. Similarly, in microbiology, a contemporaneous written record is maintained of the colony counts of a petri dish, and the record is then subject to second-person review. Document control requirements in § 211.180 pertain only to CGMP records. For more information on static and dynamic records, see 1.d. in this guidance. For PET drugs, see the guidance for industry PET Drugs—Current Good Manufacturing Practice (CGMP) for discussion of equipment and laboratory controls, including regulatory requirements for records.

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When does electronic data become a CGMP record?

When generated to satisfy a CGMP requirement, all data become a CGMP record.14 You must document, or save, the data at the time of performance to create a record in compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and 211.160(a). FDA expects processes to be designed so that data required to be created and maintained cannot be modified without a record of the modification. For example, chromatographic data should be saved to durable media upon completion of each step or injection (e.g., peak integration or processing steps; finished, incomplete, or aborted injections) instead of at the end of an injection set, and changes to the chromatographic data or injection sequence should be documented in an audit trail.

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When does electronic data become a CGMP record?

Aborted or incomplete injections should be captured in audit trails and should be investigated and justified. 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 (see §§ 211.100(b), 211.160(a), and 211.180(d)). Similarly, it is not acceptable to store electronic records in a manner that allows for manipulation without creating a permanent record. 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 entry. This would be similar to indelibly recording each entry contemporaneously on a paper batch record to satisfy CGMP requirements. The computer system described above could be combined with a procedure requiring data be keyed in or otherwise entered immediately when generated.

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Why has FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result (e.g., testing different samples until the desired passing result is obtained). This practice, also referred to as testing into compliance, is not consistent with CGMP (see the guidance for industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production). In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance.

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Why has FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

FDA considers it a violative practice to use an actual sample in test, prep, or equilibration runs as a means of disguising testing into compliance. According to the United States Pharmacopeia (USP), system suitability tests must include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied (see USP General Chapter Chromatography). System suitability tests should be performed according to the firm's established written procedures—which should include the identity of the preparation to be injected and the rationale for its selection—and the approved application or applicable compendial monograph (§§ 211.160 and 212.60).

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Why has FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

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, 211.165, and 212.60). CGMP original records must be complete (e.g., §§ 211.68(b), 211.188, 211.194) and subjected to adequate review (§§ 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)). Transparency is necessary. All data—including obvious errors and failing, passing, and suspect data—must be in the CGMP records that are retained and subject to review and oversight. An investigation with documented, scientifically sound justification is necessary for data to be invalidated and not used in determining conformance to specification for a batch (see §§ 211.160, 211.165, 211.188, and 211.192).

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

No. Analytical methods should be accurate and precise. 16 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 (see §§ 211.160, 211.165(c), 211.194(a)(4), and 212.60(a)). FDA requires complete data in laboratory records, which includes but is not limited to notebooks, worksheets, graphs, charts, spectra, and other types of data from laboratory instruments (§§ 211.194(a) and 212.60(g)(3)).

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

No. Regardless of intent or how or from whom the information was received, suspected or known falsification or alteration of records required under parts 210, 211, and 212 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 (see §§ 211.22(a), 211.125(c), 211.192, 211.198, 211.204, and 212.100). FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. “CGMP data integrity” should be included in the subject line of the email. This reporting method is not intended to supersede other FDA reports (e.g., field alert reports or biological product deviation reports that help identify drug products that pose potential safety threats).

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

Yes. Training personnel to prevent and detect data integrity issues is consistent with the personnel requirements under §§ 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties

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Is FDA allowed to look at electronic records?

Yes. All records required under CGMP are subject to FDA inspection. This applies to records generated and maintained on computerized systems, including electronic communications that support CGMP activities. For example, an email to authorize batch release is a CGMP record that FDA may review. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§§ 211.180(c) and 212.110(a) and (b)). See also the guidance for industry Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection and section 704 of the FD&C Act. Procedures governing the review of electronic records are described in chapter 5 of the Investigations Operations Manual (IOM) at https://www.fda.gov/iceci/inspections/iom/default.htm.

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How does FDA recommend data integrity problems be addressed?

FDA encourages you to demonstrate that you have effectively remediated your problems by investigating to determine the problem's scope and root causes, conducting a scientifically sound risk assessment of its potential effects (including impact on data used to support submissions to Contains Nonbinding Recommendations FDA), and implementing a management strategy, including a global corrective action plan that addresses the root causes.

This may include retaining a third-party auditor and removing individuals responsible for data integrity lapses from positions where they can influence CGMP related or drug application data at your firm. It also may include improvements in quality oversight, enhanced computer systems, and creation of mechanisms to prevent recurrences and address data integrity breaches (e.g., anonymous reporting system, data governance officials and guidelines).

These expectations mirror those developed for the Application Integrity Policy. For more detailed information, see Points To Consider for Internal Reviews and Corrective Action Operating Plans at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm.

Data Integrity – Meta Data

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Contextual information required to understand data Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the GMP activity

Examples of metadata

- date/time stamps
- user ID
- instrument ID used to acquire data, audit trails

Data Integrity – Audit Trail

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- ✓ Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- ✓ Who, what, when, and sometimes why of a record
- ✓ Example: audit trail for an HPLC run could include user name, date/time of run, integration parameters used, details of a reprocessing
- ✓ GMP compliant record-keeping practices prevent data from being lost or destroyed
- ✓ Audit trails capture: overwriting, aborting runs, “testing into compliance,” deleting, backdating, altering data

Data Integrity – Backup Data

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- True copy of original data that is maintained securely throughout the records retention period.
- Should include associated metadata
- Different from files temporarily maintained in case of computer crashes. These file do not satisfy the requirements of 211.68(b) to maintain a backup.

Data Integrity – Exclusion of Data

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- ✓ Any data (including metadata) must be evaluated by the quality unit as part of release criteria and maintained.
- ✓ Any exclusion of data from the release criteria decision making process must be scientifically justified (See FDA's OOS Guidance)
- ✓ Bottom line: be very careful.

Data Integrity – Computer Access

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- ✓ Must ensure that any changes to records be made only by authorized personnel
- ✓ FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means (e.g. limiting permissions)
- ✓ System administrator should be different from those with substantive responsibility
- ✓ Shared login accounts are problematic.

Data Integrity – FDA Observations

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- ✓ Warning letter: Systemic data manipulation across the facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.
- ✓ "Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events."

Data Integrity – Review of Audit Trail

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- ✓ FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.
- ✓ Audit trials subject to regular review should include changes to:
  - ●history of unfinished product test results
  - ●sample run sequences
  - ●sample identification
  - ●critical process parameters
- ✓ FDA recommends routine scheduled audit trial review based on complexity of the system and its intended use
- ✓ Personnel responsible for record review should review audit trails that capture changes to critical data as they review the rest of the record

Data Integrity – FDA observations Audit Trail

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- ✓ Raw data were being deleted or altered on IR spectrometer
- ✓ No access controls
- ✓ No active audit trials on IR
- ✓ File names altered to make it appear tests supports additional lots of API
- ✓ Warning letter stresses lack of audit trails for lab instruments and turning off audit trails

Data Integrity – Control on Blank Form

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- ✓ Blank forms (e.g. worksheets, laboratory notebooks) should be controlled by the quality unit or by another document control method
- ✓ Numbered sets of blank forms may be issued and should be reconciled upon completion of the activity,
- ✓ Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement.

Data Integrity – Misuse of Blank Form

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- ✓ "Our investigator observed many copies of uncontrolled blank and partiallycompleted CGMP forms … without any accountability or oversight of your quality unit."
- ✓ "[A] supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document." FDA rejects firm's argument that OOS form was not an "official document" until it was placed in the QA system. Firm did not follow firm's SOPs.
- ✓ "Your quality unit is responsible for reviewing and approving these critical production records to ensure that, if an error occurred, a comprehensive investigation is conducted. Uncontrolled destruction of CGMP records also raises concerns, because retention of CGMP records must follow established procedures approved by your quality unit."

Data Integrity – GMP Document

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- ✓ All data generated to satisfy a GMP requirement becomes a GMP record.
- ✓ Firms must document or save the data at time of performance
- ✓ Processes must ensure that maintained data cannot be modified.
- ✓ Not acceptable to store data in temporary memory or on pieces of paper that will be discarded after the data are transcribed to a lab notebook
- ✓ Computer systems, such as LIMS or Electronic Batch Record systems, can be designed automatically save after each separate entry

Data Integrity – Warning Letter

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- ✓ January 2018:
- ✓ Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

  A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.

  B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

  C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

Data Integrity – Warning Letter

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- ✓ January 2017
- ✓ Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.
- ✓ In response to this letter, provide the following:

Data Integrity – Warning Letter

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A.

A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the manufacturing and laboratory data integrity deficiencies.

We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

Data Integrity – Warning Letter

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B.

A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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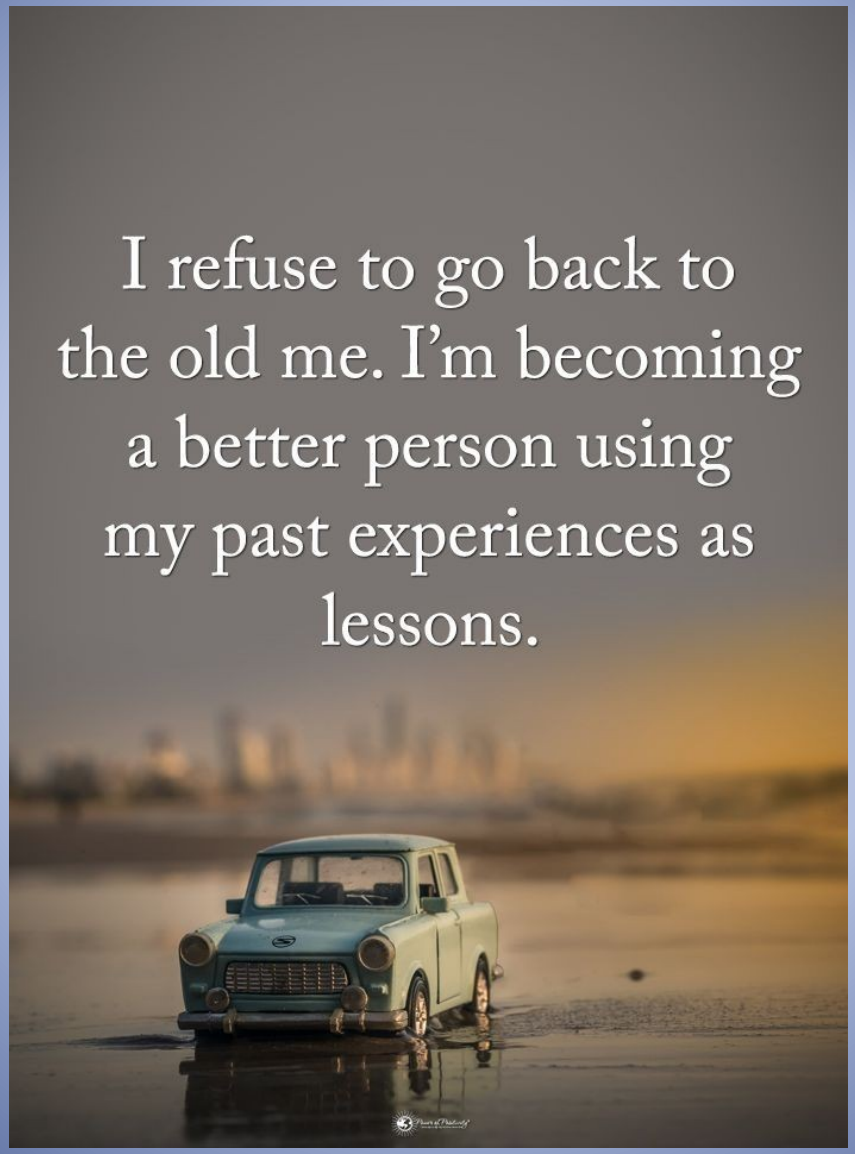
I refuse to go back to
the old me. I'm becoming
a better person using
my past experiences as
lessons.

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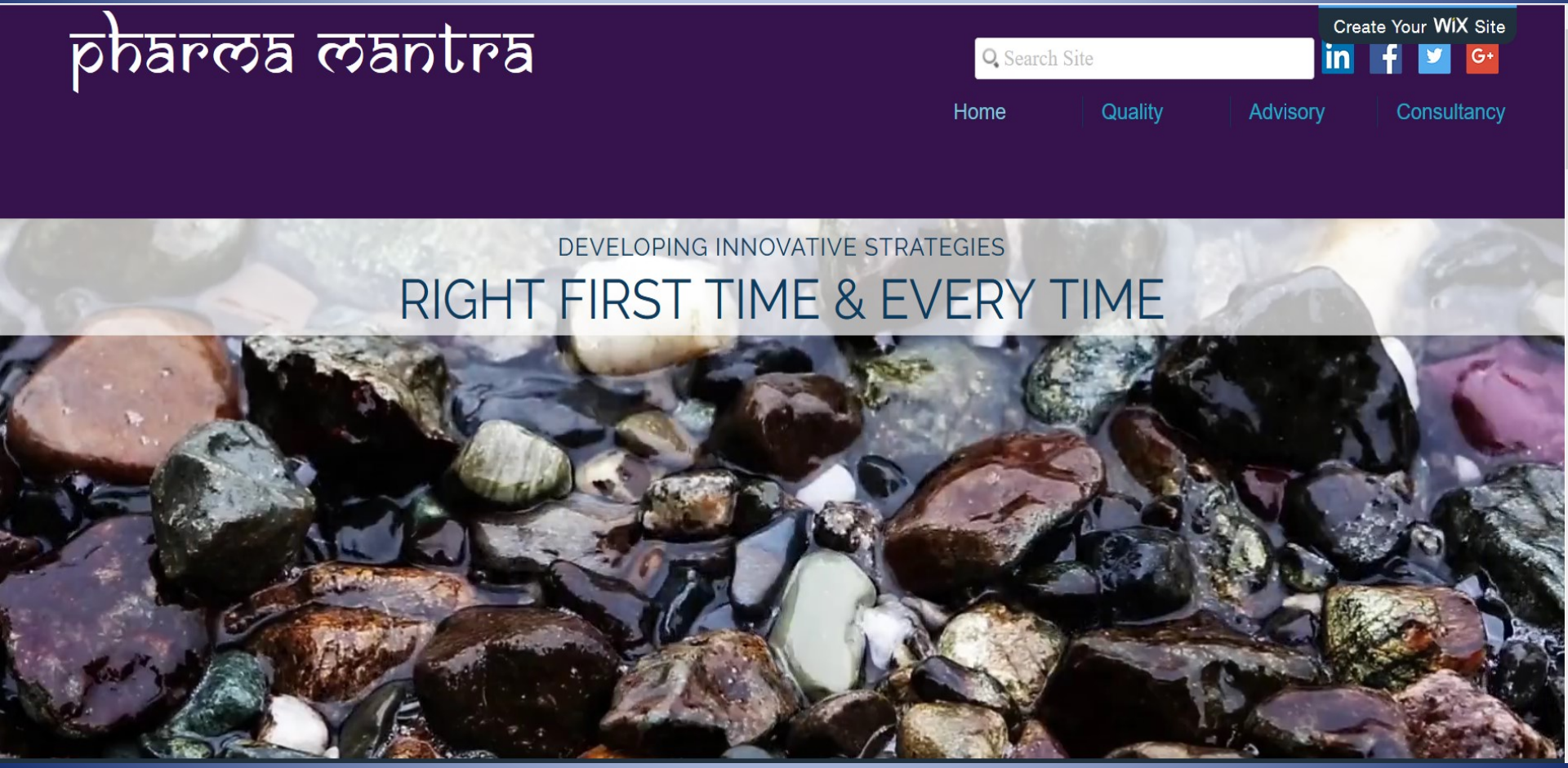

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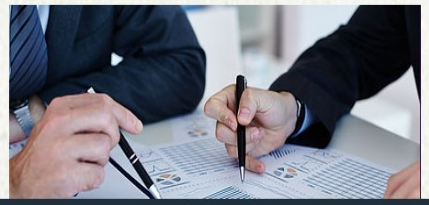
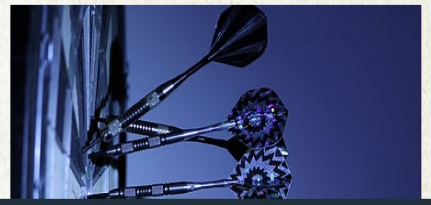
Steering organization through complex Quality & Regulatory challenges, remediation, transitions & building an empowered Quality Operations Team which is capable and empowered to deliver results within highly competitive products and regulatory environment.

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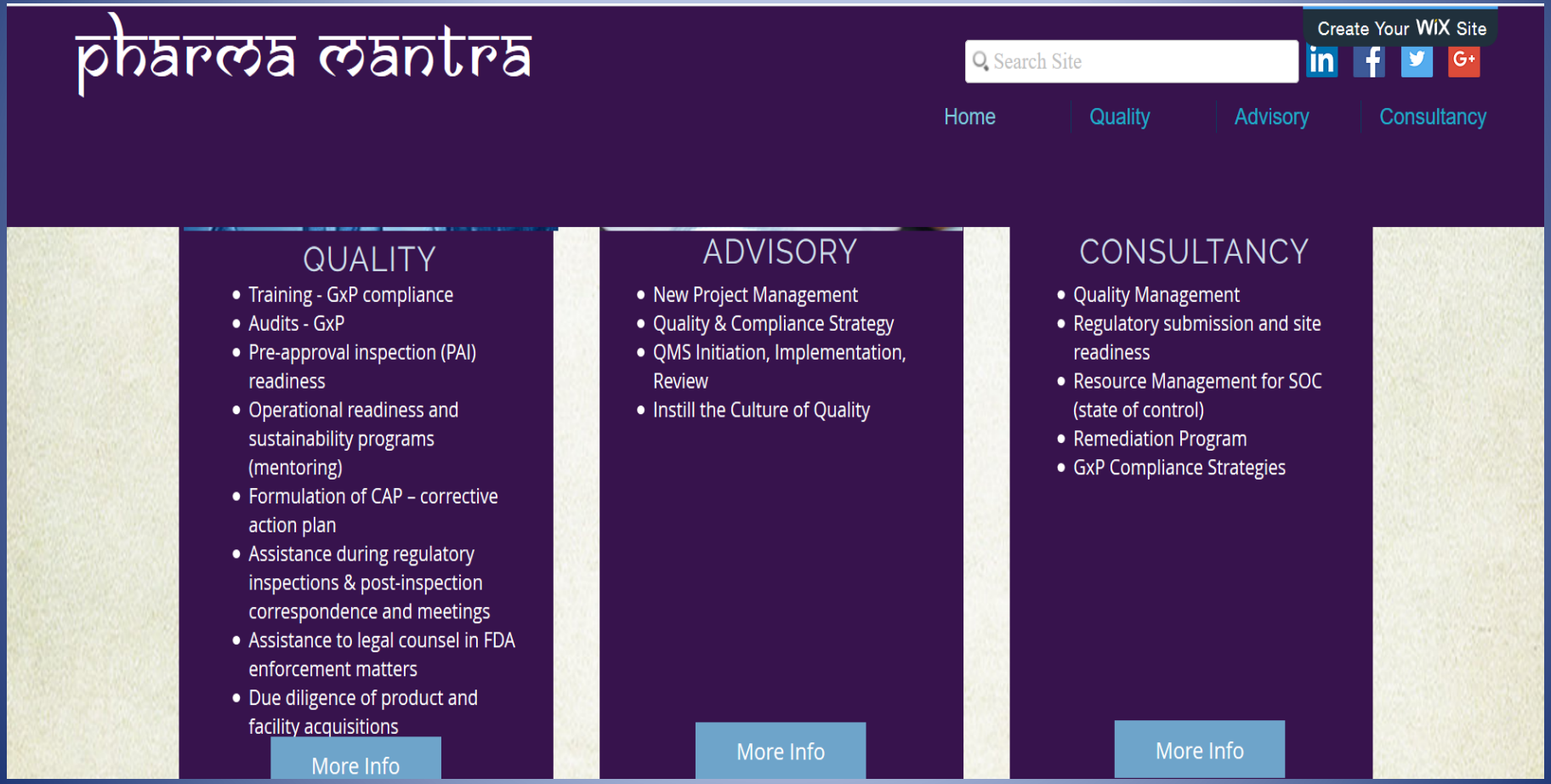

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CONTACT US

Udaykumar Rakibe

Mobile: +917756848484

Email: pharmantra.expert@gmail.com

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Udaykumar K. Rakibe
Founder

M.Pharmacy & MBA from Pune University – was mandated and given the task to execute and spearhead the proactive remediation in 2006 by Ranbaxy Lab. Ltd. In late 2011 he was recruited by Intas Pharma. to create a self-sustaining quality management system and enhance inspection readiness. Further, in 2013 he was hand-picked & recruited by Wockhardt Ltd., as Senior Vice President – Quality, to turn around the Quality Management, lead and manage the remediation of Quality initiatives.

Udaykumar is a quality professional with a dynamic career steering organizations through complex Quality & Regulatory challenges, transitions, building an empowered and talented workforce in the cross-cultural environment within highly competitive products and regulatory environment.

He began his career in Quality function in the Executive in-process QA with Glenmark Pharma Ltd. and then moved to different levels and organization spanning 26 plus years of hands-on and hardcore experience in the pharmaceutical regulatory environment. He has gained the domain experience in Quality by working 20 years' in Quality operations- out of twenty years last 11 years focusing and leading the Quality & Regulatory remediation. He has 7 years experience in Corporate Quality functions, overseeing the Developmental & filing of - Clinical, Analytical, Formulation, Devices. Has setup the Global Quality organization for the Contact Manufacturing in regulated and semi-regulated markets He has worked as a senior member of the Quality Team with Ranbaxy Labs Ltd., Dabur Pharma Ltd., Gland Pharma Ltd.,