CONVAL group

Data Integrity for Auditors

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Agenda

- Fundamental concepts of Data integrity
- Process centric organization
- What is the "Data Manipulation triangle"
- Why DI problems occur
- Data Integrity Maturity Model (DIMM)
- Warning letter trend
- Q&A

What is Data Integrity

- It is the **trustworthiness** of data through the assurance that data records are accurate, complete, intact and maintained within their **original context**.

Guiding principles Data Integrity

- Measures should be implemented to ensure that GxP regulated computerized systems and data are adequately and securely protected against willful or accidental loss, damage or unauthorized change.

- Such measures should ensure the continuous control, integrity, availability and where appropriate the confidentiality of regulated data.

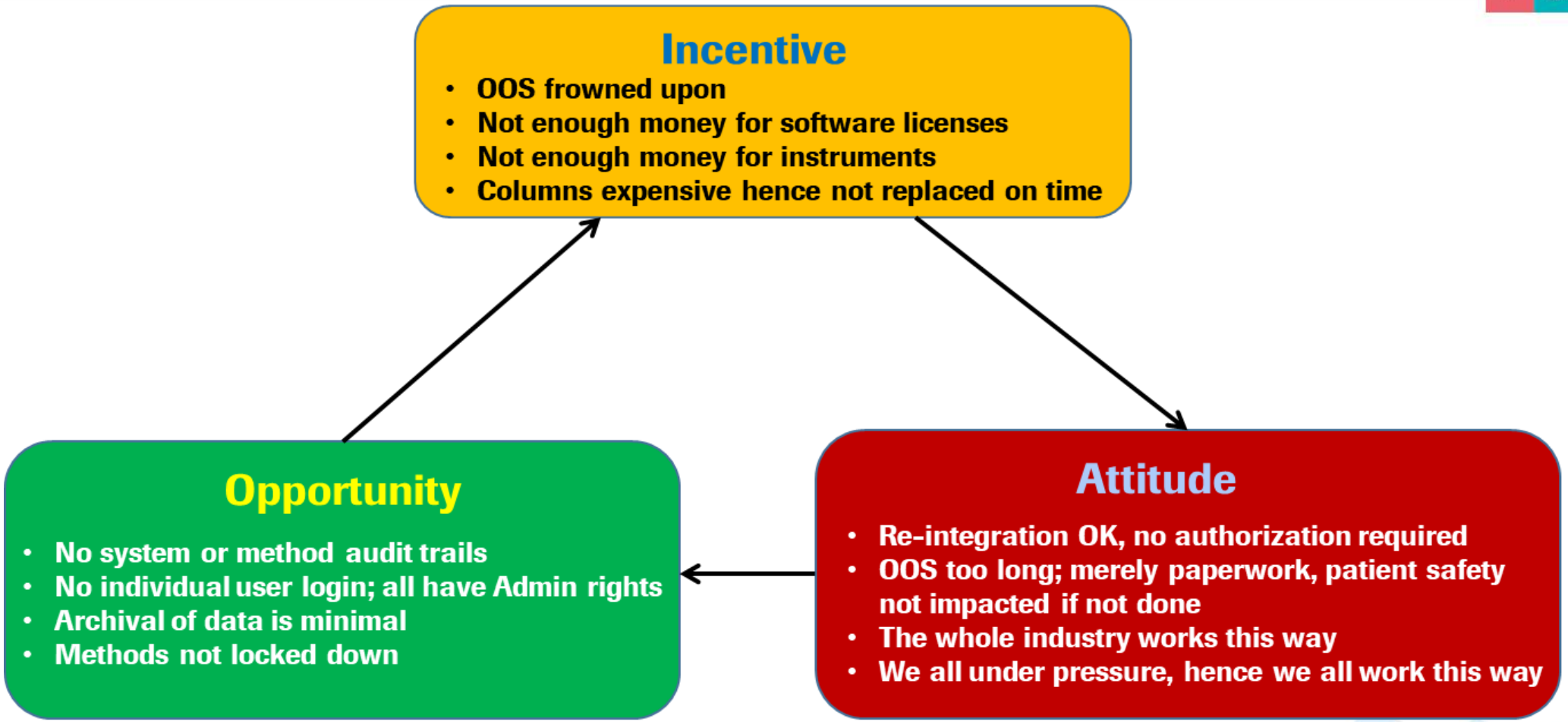
How is it realized

- Data integrity is solely dependent on the company's business process
- In a process centric company
  - ✓ Leadership leverages processes to derive business outcomes
  - ✓ Also focus on associated elements: people, their supervisors and leadership
  - ✓ Better understanding by employees that problem solving and meeting customer requirements is a key part for success

Attributes of a process centric organization

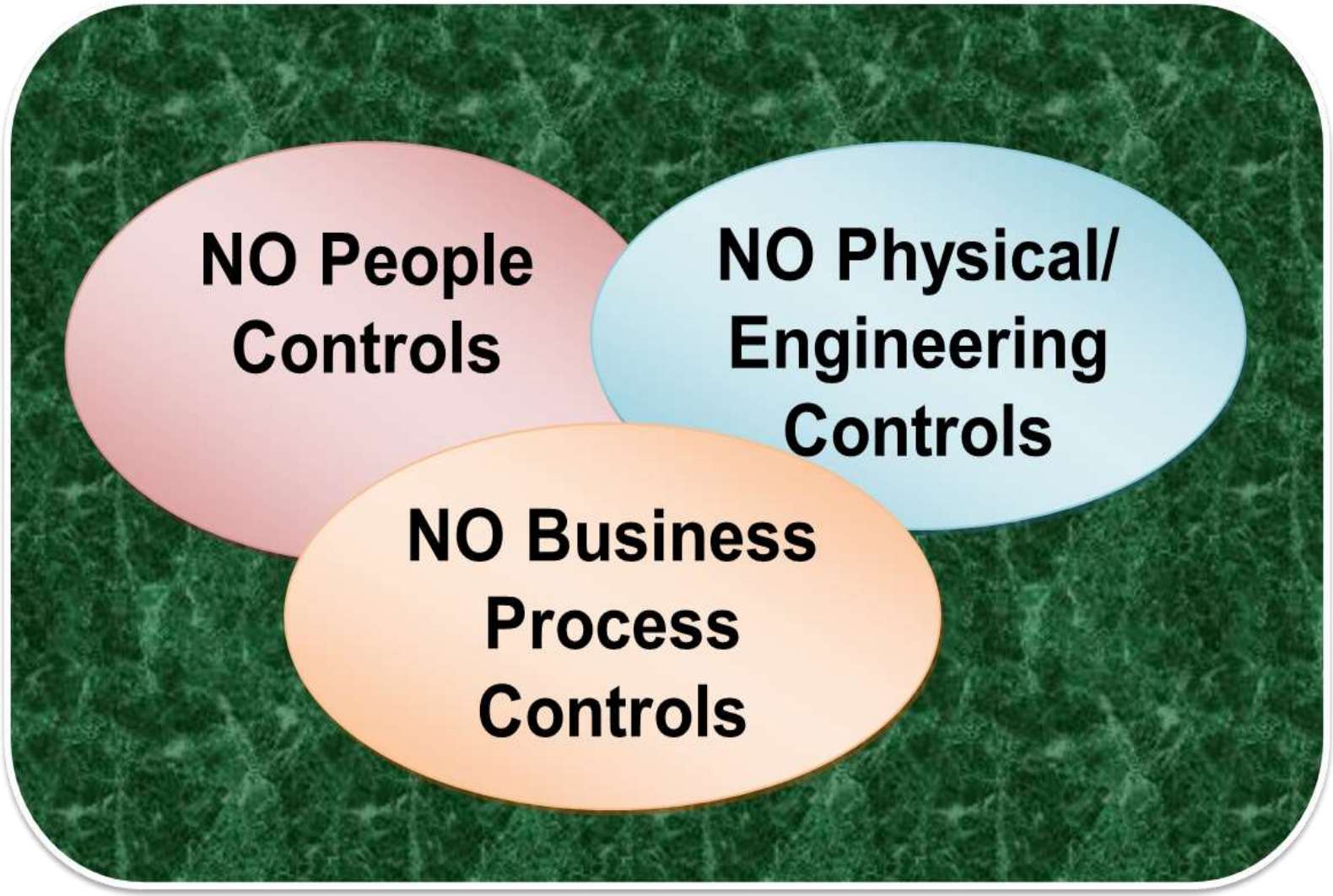
- Clarity of key processes
- Processes have well defined ownership
- Performance outcomes gets measured (KPIs etc.)
- Process improvements move up a maturity continuum
- Organizational culture (values, the 5P model)
- Employee empowerment and accountability

Data manipulation triangle



"The Fraud Triangle" Occupational Fraud and Abuse, by Joseph T. Wells, 1997

Why Data Integrity problems occur



People controls

CAUSE

- **Company Culture**
  - Blame, fear
  - Production targets
  - No employee awareness
  - Why they do what they do
- **Process**
  - Complicated
  - Overlapping
  - No stakeholder involvement
- **Training**

SOLUTION

- **Supervision**
  - Close supervision
  - Walk the floor
  - Review & simplify SOPs
  - Blame free culture
  - Admit mistakes
  - Automate unhesitatingly
- **Training**
  - Mandatory DI
  - Ethics,
  - External

Design controls

CAUSE

- **Physical controls**
  - No tracking of entries/exits
  - Monitor data storage areas
- **Design controls**
  - Stakeholder involvement
  - DI not part of design
  - Inadequate validation & testing
  - Aging systems
  - Alarming of CQA & CPP
  - Sequencing interlocks

SOLUTION

- **Design such that**
  - People controls design priority
  - Operational complexity is reduced
  - Involve stakeholders
- **Across enterprise**
  - Uniform design policy
  - Common platform technologies
  - Share DI lessons learned

Business Process controls

CAUSE

- **Organizational**
  - Fragmented & activities overlap
  - Roles & responsibilities overlap
  - Poorly communicated and understood Policies and Standards
- **Compliance literacy**
  - No awareness
  - Inadequate internal audits

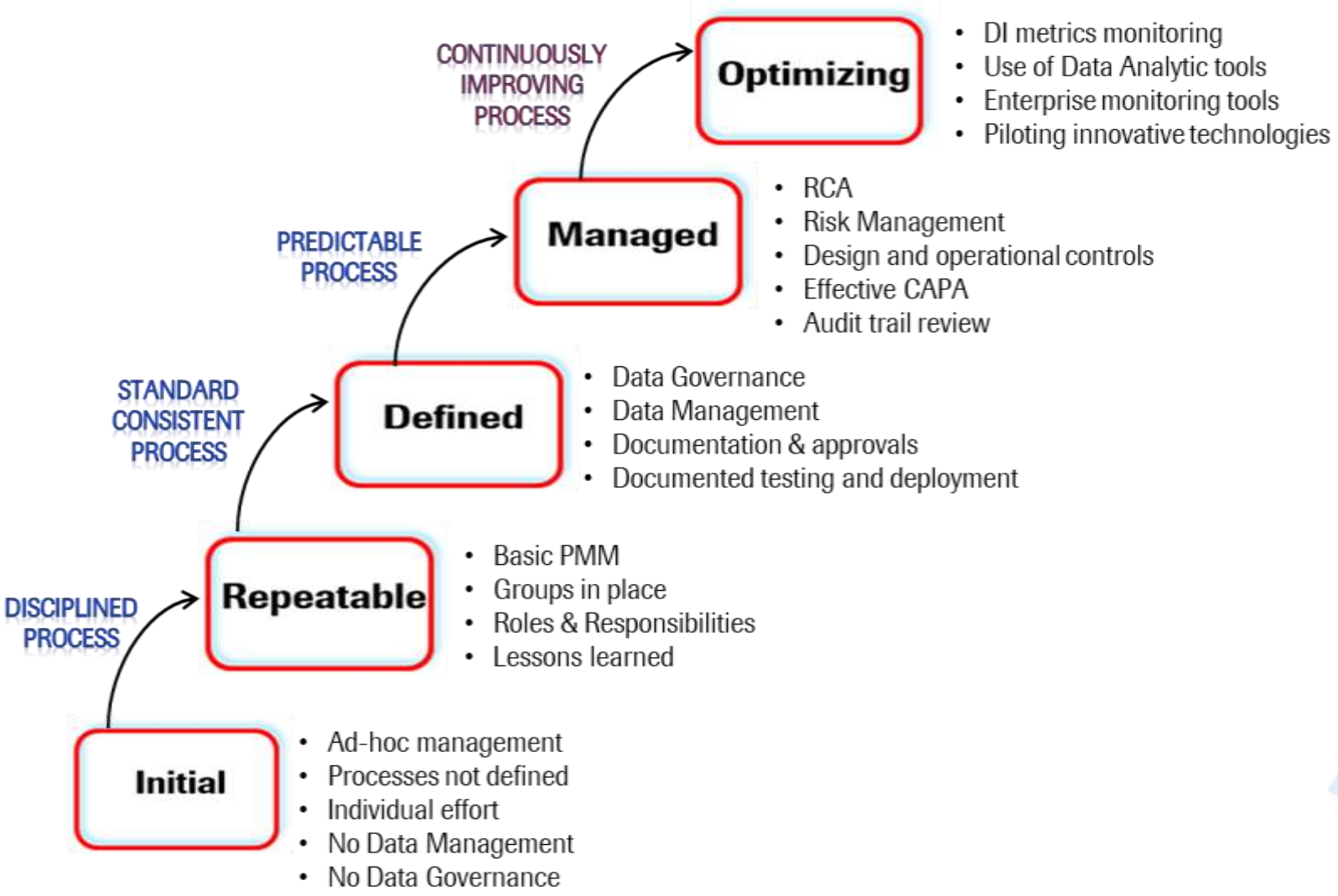
SOLUTION

- Regular review of Policies, Standards & SOPs
- Centralized audit co-ordination
- Use common audit tools
- Senior management review of audit outcomes
- DI programs performance metrics

In summary - Top contributing factors for DI issues

- Employee ignorance and dis-involvement
- Company culture; blame and fear
- Complexity and confusion of Roles & Responsibilities
- Leadership/managements compliance literacy

Data Integrity maturity model



Data Integrity warning letters

	2019	2020	2021	2022
211.22	**20.31**	**25.40**	**31.58**	14.13
211.68	6.25	6.35	10.53	10.87
211.100	**23.44**	**26.98**	**26.32**	**18.48**
211.160	7.81	9.52	10.53	**16.30**
211.180	2.34	0.00	0.00	5.43
211.188	6.25	1.59	5.26	6.52
211.192	**27.34**	**23.81**	**15.79**	**27.17**
211.194	6.25	6.35	0.00	1.09

Agenda

- Drugs & Cosmetics Act and Rules 1945, As Amended upto Dec. 2016
- Draft GSR 999 Oct. 2018 Schedule M

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Clinical Trials Submissions to Licensing Authority

- Licensing Authority evidence is based on *data* justifying that the patent or propritary medicine....
- *Data* on the stability of drugs.....so furnished.
- *Data* provided or generated on the drug is inadequate, intimate the applicant in writing.....
- *Data* analysis.....missing *data*.....*data* for treatment failures
- Permissions on the basis of data available from other countries.....
- Search and sieze *any record, data*, document, books, investigational drugs...
- ..enter the premises to inspect *any record, data* or any document.....

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

For Whole Human Blood and Blood Components

- *Data* on the stability of whole human blood....

- For New Drug Applications
- Bio-availability, dissolution and stability-study *data*
- Animal toxicity *data*
- *Data* on pharmacokinetics....
- *Data* on safety and efficacy....
- Stability *data*....
- Bio-equivalence *data*

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Schedule L Good Laboratory Practices and Requirements of Premises and Equipments

- ….involves all *raw data*...
- A standardized register....along with its *raw data* and SOPs...
- Record keeping, reporting, storage and retrieval of *data*...
- Handling of *data* including use of *computerized data system*...
- Analytical *data* methods...
- Data handling, storage and retrieval
- Raw data refers to lab notebooks, work sheets, analysis sheet, records, photos, software, drawings, computer printouts....recorded data for automated equipments...

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Schedule L Good Laboratory Practices and Requirements of Premises and Equipments

- A *single line shall strike through the data* being changed; the correct information shall be recorded along with the old data and the *reason of change*. The analyst making the change shall be identified by his *signature with date*. In case of automated data collection system, the person responsible shall be identified at the *time of data output*. The *original entry* must be saved and the system have *audit trial* for all the data.
- *Data integrity and security* shall be maintained, and the data shall *not be accessible to any unauthorized person*.
- The archive shall provide a suitable environment that will *prevent modification, damage, or deterioration and/or loss.*
- (d) The condition under which the original documents are stored must ensure their *security and confidentiality*,

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Schedule L Good Laboratory Practices and Requirements of Premises and Equipments

- *Paper documents* shall not be kept for long periods under high humidity and *raw data in the form of tape* and discs are to be preserved with care,
- (f) In case of storage of only optical disc, the *life of disc* shall be longer than the storage time,
- (g) *Raw data on thermal paper* might fade away with time; therefore, a *photocopy of the thermal paper* shall also be retained in the archive.
- (h) *Time for which records are retained* shall be prescribed in the documents.

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Schedule M Good Manufacturing Practices

- The manufacturer shall establish documented procedures to determine, collect and *analyze appropriate data* to demonstrate the suitability and *effectiveness of the quality management system* and to evaluate whether improvement of the effectiveness of the quality management system can be made.
- This shall include *data generated* as a result of monitoring and measurement and from other relevant sources.

Drugs and Cosmetics Act and Rules, 1945 as Amended upto Dec. 2016

Schedule M Good Manufacturing Practices

- Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating to the system in use *shall also be available in a hard copy to facilitate checking of the accuracy of the records*. Wherever documentation is handled by electronic data processing methods, *authorized persons* shall enter or modify data in the computer. There shall be record of changes and deletions. *Access shall be restricted* by 'passwords' or other means and the result of entry of critical data shall be independently checked. *Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available*.

Draft GSR 999 Oct. 2018 Schedule M

Schedule M Good Manufacturing Practices

- ……to ensure the existence of *documented evidence*, *traceability*, and to provide records and an *audit trail* that will permit investigation. It ensures the *availability of the data* needed for validation, review and statistical analysis.
- Where documents require the *entry of data*, these entries shall be *clear, legible and indelible (refer ALCOA+)*. Sufficient space shall be provided for such entries.
- If documentation is handled by electronic data-processing methods, *only authorized persons shall be able to enter or modify data in the computer system*, and there shall be a *record of changes and deletions*; access shall be restricted by passwords or other means and the entry of critical data shall be independently checked. *Batch records* stored electronically shall be protected by *back-up* transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the *period of retention, the data are readily available. (Backup, Restoration, Archival)*

Draft GSR 999 Oct. 2018 Schedule M

Schedule M Good Manufacturing Practices (Section 22: Computerized System)

- *GMP-related computerized systems shall be validated*. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
- Computerized systems shall have *sufficient controls to prevent unauthorized access or changes to data (Role Based Access Control)*. There shall be *controls to prevent omissions in data (Data Loss Prevention)* (e.g. the system being turned off and data not captured). There shall be a record of any *data change made, the previous entry, the person who made the change (Audit Trail Review)* and when the change was made.

US-FDA Explanation on Audit Trail Review:

- 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. For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit. FDA recommends a quality system approach to implementing oversight and review of CGMP records.

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US-FDA Explanation on Audit Trail Review Frequency:

- 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.
- Audit trails may be reviewed as a list of relevant data, or by an 'exception reporting' process. An exception report is a validated search tool that identifies and documents predetermined 'abnormal' data or actions, that requires further attention or investigation by the data reviewer.

Draft GSR 999 Oct. 2018 Schedule M

Schedule M Good Manufacturing Practices (Section 22: Computerized System)

- Where *critical data are being entered manually*, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or *by the system itself*.*(Technical Controls – Configuration Specifications) (All available functions of a component should be specified and documented. Their fundamental system behaviour independent of the use case should be described. Incorrect behaviour in the sense of mal-operation should never initiate an unintentional (unknown and unexpected) mode.*
- A back-up system shall be provided so that there is no *permanent loss of records due to system breakdown or failure*. Means of ensuring *data protection* shall be established for all computerized systems. *(Data backup and restoration testing, Recovery Time Objective, Recovery Point Objective)*
- *Data from continuous monitoring* of certain production processes (such as fermentation) shall form part of the batch record.

Draft GSR 999 Oct. 2018 Schedule M

Schedule M Good Manufacturing Practices (Section 22: Computerized System) Laboratory Control Records

- A complete record of *all raw data generated during each test*, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested.
- Any OOS result obtained shall be investigated and documented according to a procedure. This procedure *shall require analysis of the data*, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling and/or retesting after OOS results shall be performed according to a documented procedure.

Summary

"Quality **cannot be** controlled. Quality **must be built** into the system."

Questions

Thank You