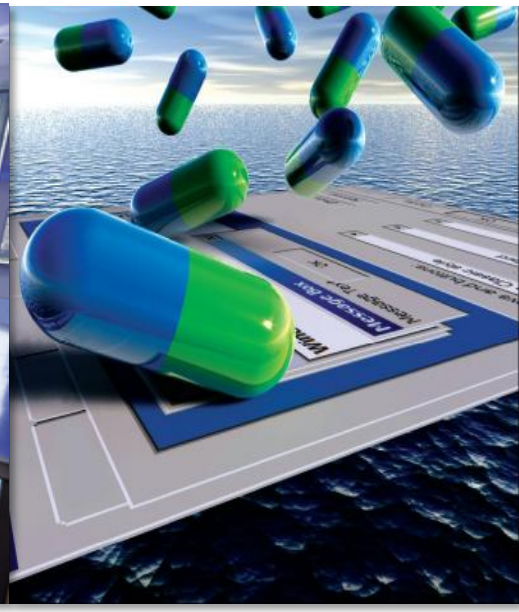
Data Integrity

A Paradigm shift in regulators approach



Nitish Chakravarty

Presentation Overview

1. What is Data Integrity and it's importance
2. Common Citations: Data Integrity
3. Regulatory Concerns...
4. Data Integrity….People, Process & Technology
5. How to avoid data integrity…

Q & A Session

What is Data Integrity and it's importance

What is data integrity

- The extent to which all data are complete, consistent, and accurate throughout the life cycle.
- From Initial data generation and recording through processing (including transformation or migration), use, retention, archiving, retrieval and destruction.

(MHRA guidance Mar 2015)

- Data integrity– requirements for complete, consistent, and accurate data throughout CGMP

(USFDA Data Integrity Workshop June 2016)

What is Data Integrity and it's importance

Data integrity importance

- cGMP – minimum requirements.
- Everything we do in the regulated industry is supported by appropriate data.
- The data creates the trust required to discover, develop, commercialize, and distribute drugs successfully.
- Records, paper or electronic, are the foundational evidence that our products are safe and effective.

Other Important Concepts

- Meta Data
- Audit Trail
- Static Vs. Dynamic Records
- Back Up
- Systems

Common citations: Data Integrity (1/2)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Your firm failed to document production and process control functions ***at the time of performance*** (21 CFR 211.100(b)).
  - Cited in 2 warning letters
  - Operator recorded the amount of material dispensed before it was dispensed
  - Employees admitted they do not record activities at the time of performance
  - QA employee signed as reviewing and releasing a batch when he did neither

7

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Your firm did not document laboratory activities ***at the time of performance*** (21 CFR 211.160(a)).
  - Cited in 3 warning letters
  - Pre-dating or backdating laboratory records
  - Occurred for assay, loss on drying, sample weighing, and stability testing

9

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Ten bags of torn or partially destroyed original records including CAPAs, preventative maintenance forms, and calibration records were found
- Raw data was written on scratch paper and sometimes differed from the data in the BPR
- Correction fluid was used on production records

11

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Cited in numerous warning letters:
  - Audit trails were disabled
  - A shared username and password was used by many analysts
  - Users were able to manipulate, delete, or overwrite electronic raw data
- Firm's laboratory practice is to print chromatograms and delete electronic raw data files

16

Common citations: Data Integrity (2/2)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Cited in numerous warning letters as failure to retain complete data:
  - "trial" sample injection data was not kept as part of the data for a batch
  - Sample weights, sample preparation and sample dilutions were not retained
  - Deleted data detected in audit trails
  - Overwriting data
  - Ripped up data found in the garbage

18

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Microbiological data missing:
  - Not reporting microbiological counts
  - Hundreds of environmental monitoring samples were not collected
  - Some microbiological sample plates/tubes were missing from the incubator
  - No microbiological testing was conducted; however, microbiological test results were reported on the certificate of analysis (COA)

19

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Firm deleted all electronic raw data supporting HPLC release testing
- Standards were injected and used as sample results
- Duplicate logbooks were kept
- Complete raw data to support test method validation was not retained
- Integration parameters for HPLC analysis were not retained

21

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Most Common Citation

- Certificates of analysis missing data:
  - Data on the COA sent with the batches was different than the COA the firm retained on file
  - COA retest date was changed to an expiration date and listed as eleven months later
- No raw data in support of results reported on COA
- Samples with no identification were discarded during the inspection

20

Impact of Non-Compliance

- *Risk to patients.*
- *Credibility / Image / Business Loss.*
- *Cultural and Ethical Issue.*
- *Dossier Filling / ANDA / DMF affected.*
- *Expenditure increased to remediate and hire 3rd party consultants.*

Impact of Non-Compliance

Regulatory Concerns… (1/2)

Recent Concerns raised by USFDA, MHRA, EMA and other agencies…

Number of WLs that have major focus on DI has increased significantly since 2010…

- *From 2 in 2010 to 10 in 2014…*
- *17% WL in 2014*
- *30% WL in 2015*

Most problems centered around

- *Test results not being entered when batches were in production*
- *Failure to retain raw data & Questionable Data*

Regulatory Concerns… (2/2)

Past several years have brought increased concern & level of regulatory attention to issues surrounding…

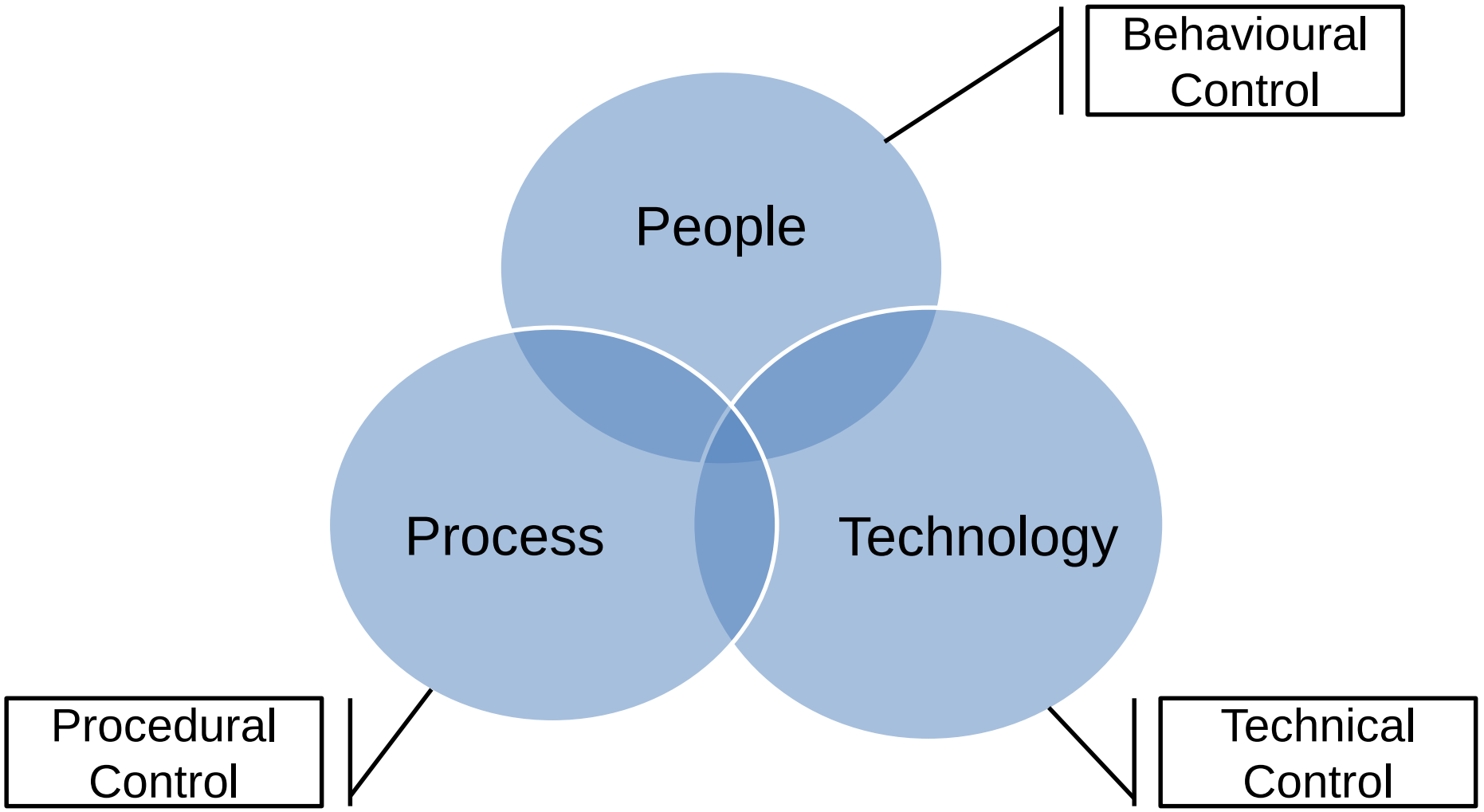
- *Access Control to electronic systems..*
- *Audit trail reviews..*
- *Backing up of data..*
- *Supplier quality management..*

The top deficiencies related to data integrity found by FDA in 2015..

- *Failure to include complete data*
- *Audit trail, data control and sharing password…*

Regulatory will assume that non- compliance or faulty data is ***intentional and not accidental****…*

Data Integrity….People, Process & Technology



Data Integrity….People

Humans are integral part of our processes.

Human errors have become the larger percentage of all errors.

Reason for Human Errors;

- Lack of effective training
- Fatigue
- Ignorance
- Too many steps
- Poorly design equipment
- Too much work

Management factors impacting Human Errors;

- Culture of fear and blame – where error are hidden
- Inadequate personnel
- Inadequate equipment
- Inadequate resources
- Wrong KPIs

Data Integrity….ALCOA

A — Attributable
- Clearly indicate who recorded the data or performed the activity
- Signed / Dated
- Who wrote it / When

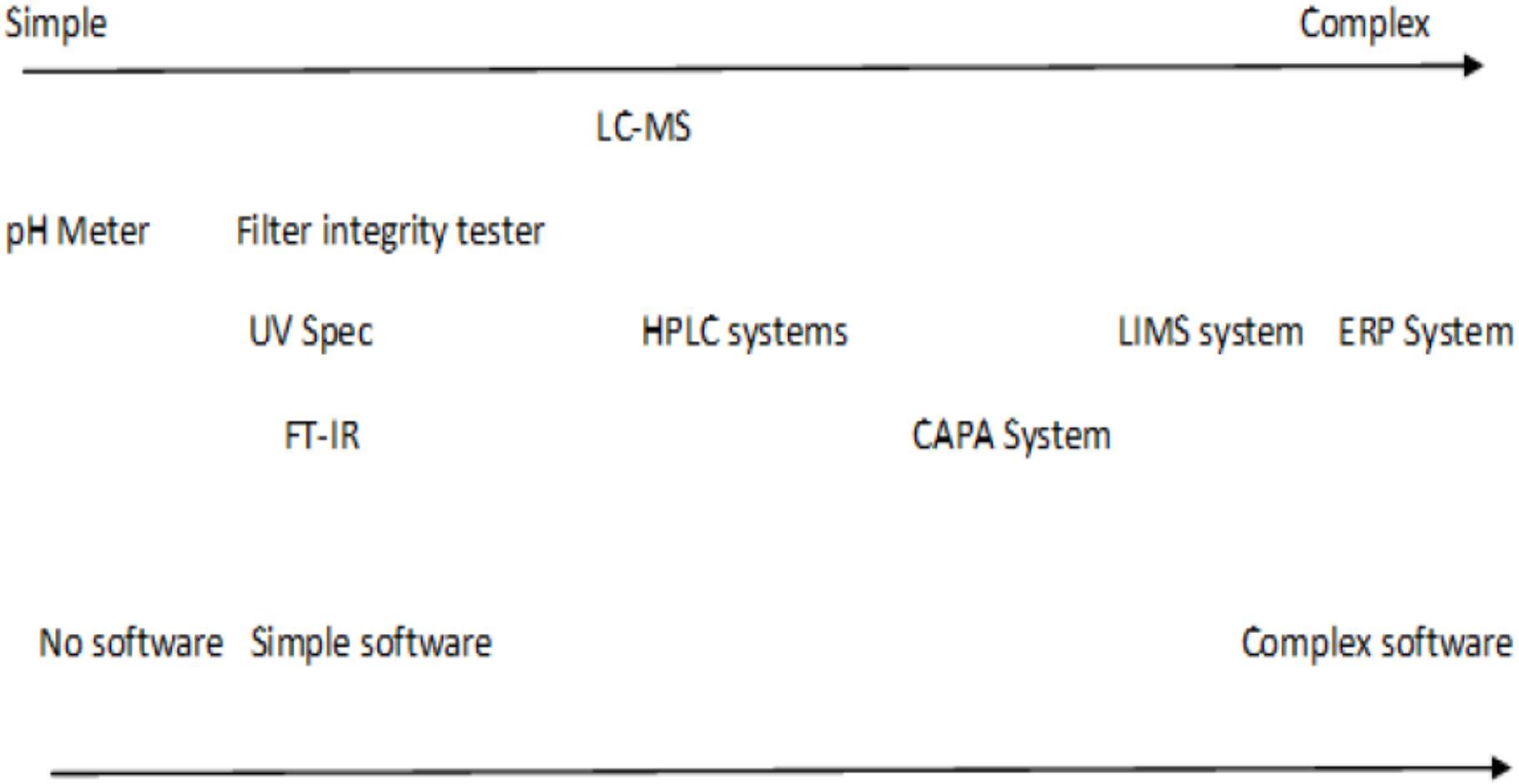
L — Legible
- It must be possible to read or interpret the data after it is recorded
- Permanent
- No unexplained hieroglyphics
- Properly corrected if necessary

C — Contemporaneous
- Data must be recorded at the time it was generated
- Close proximity to occurrence

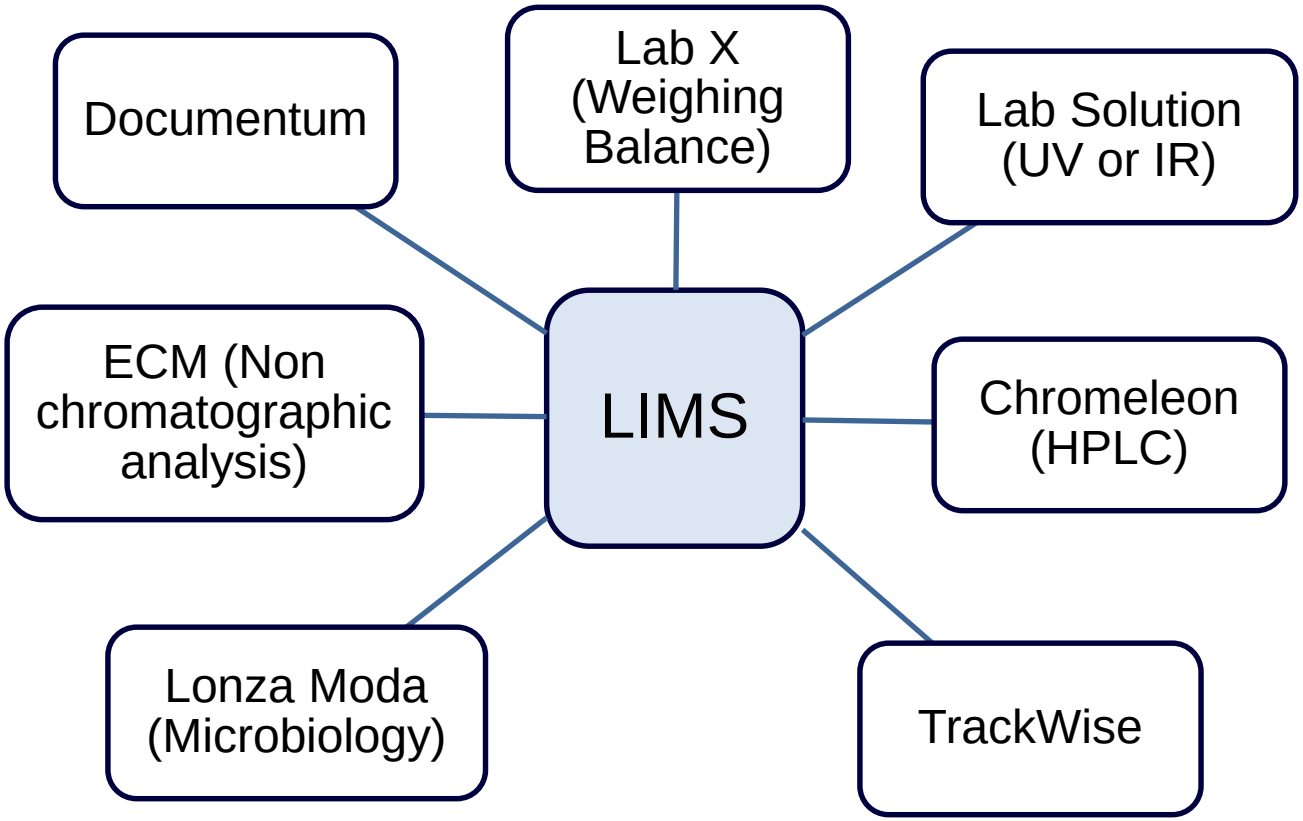
O — Original
- Data must be preserved in unaltered state.
- If not why not
- Certified copies

A — Accurate
- Data must correctly reflect the action / observation made
- Data checked where necessary
- Modifications explained if not self evident

✓ Automation….Paper to Electronic Conversion



✓ Application (Software) used for laboratories



How to avoid data integrity…

- ✓ Mistake Proofing is Key: POKA-YOKE
  (Japanese term which means mistake proofing)
- ✓ Look for gaps in how you control your records
- ✓ Ensure employees have appropriate user privileges
- ✓ Audit your data in a risk-based manner
- ✓ Verify the authenticity of your contractors' data
- ✓ Culture Strengthens Data Integrity – Human Errors

  (Violations, Mistakes, Lapses & Slips)

MES (Manufacturing Execution System)

A manufacturing execution system (MES) is an information system that connects, monitors and controls complex manufacturing systems and data flows on the factory floor.

- Improved regulatory compliance
- Elimination of paperwork and manual data-entry processes
- Increased customer satisfaction
- Improved supply chain visibility
- Reduced order lead time
- Lower labor costs

MES (Manufacturing Execution System)

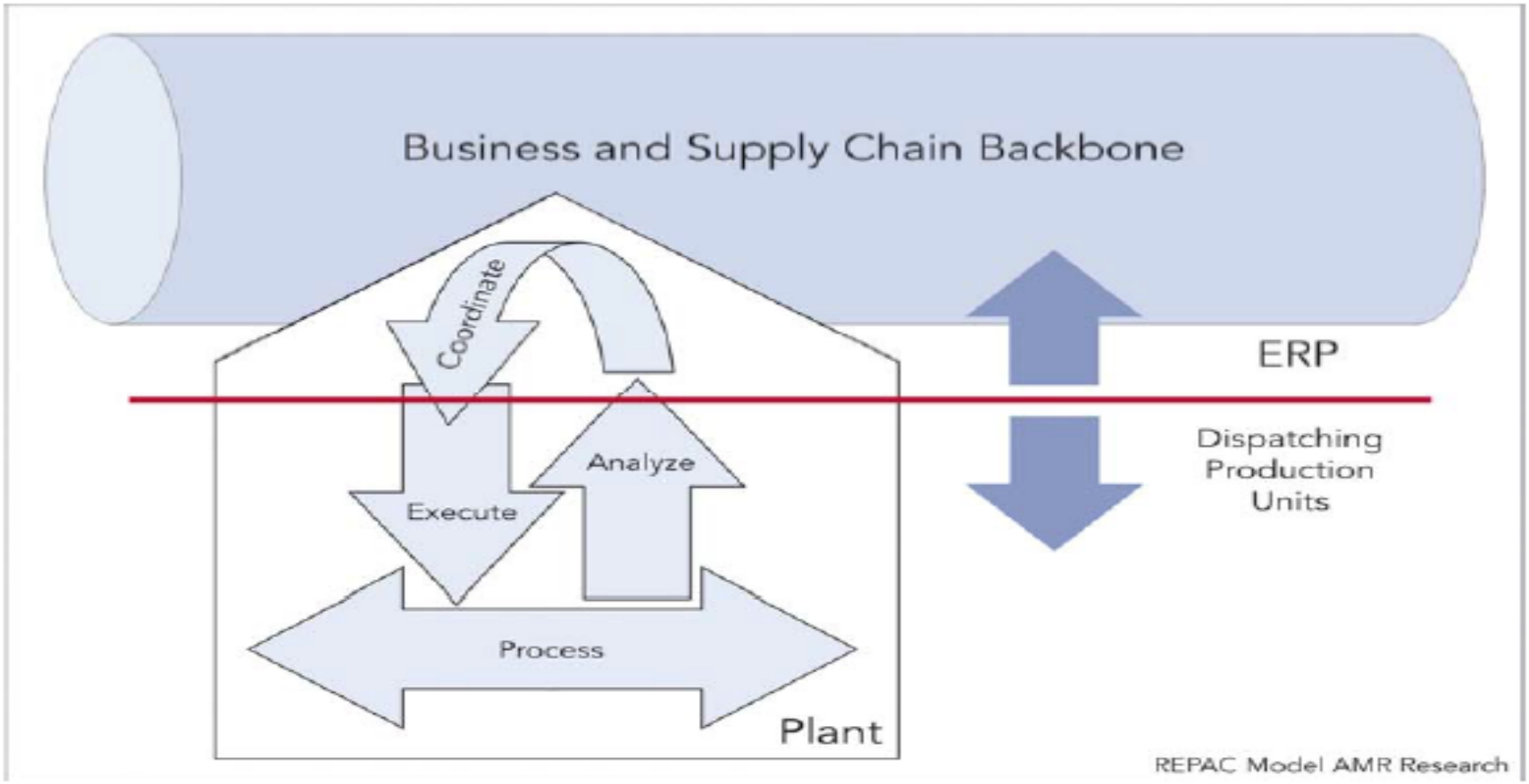


Figure 1: The REPAC model (Ready, Execute, Process Control, Analyze, Coordinate)

eBMR (Electronic Batch Manufacturing Record)

- Efficient way to capture data, batch production management, maintain data security and integrity, and report production.
- Compliance to cGMP requirements, such as FDA 21 CFR part 11

MES and e BMR ensures

- The right material has been used.
- The materials have been weighed as per the recipe.
- SOPs and checklist have been followed for machine preparation.
- Ensure sequencing of operations as per SOPs.
- In process parameters are monitored and recorded at stipulated intervals.

ALCOA of Data Integrity in MES

- Attributable:
  - User has to login using their own credential. MES records the batch operation with the user. At decision and data stamping stage it asks for electronic signature of production and QA.
- Legible:
  - No hand written data recording, Data is reordered by computerized system.
- Contemporaneous:
  - Every operation, Decision, Excursion by default recorded along with very high accuracy date and time, including time zone of world clock. Date and time of MES system is synchronized with GPS clock.
- Original:
  - Data from SAP, LIMS, machines, equipment exchanged electronically through seam less integration.
- Accurate:
  - Data correctly reflect the action / observation made and modifications recorded in the event logs.

Batch Manufacturing process with MES

Recipe Created , Approved and validated in MES

MES receives process order from SAP through MES-SAP interface

A recipe for process order is sent for electronic approval of stake holders

Upon recipe approval, MES releases process order for batch manufacturing

Based on process order MES identifies the material & quantity using barcode label and send consumption details against the process order to SAP

MES generates the barcoded label for dispensed material for next stage

Material is first identified using barcode and then next stage of batch processed

Batch Manufacturing process with MES

MES ensures the room, environmental and equipment's parameter as defined in recipe and violations are raised as excursion

After completion of a batch process stage as per receipe, MES collects all the data from DAS (Data Acquisition System) including alarms

Production and QA are prompted to review excursions and data received electronically and ensures adherence using electronic signature of Production and QA

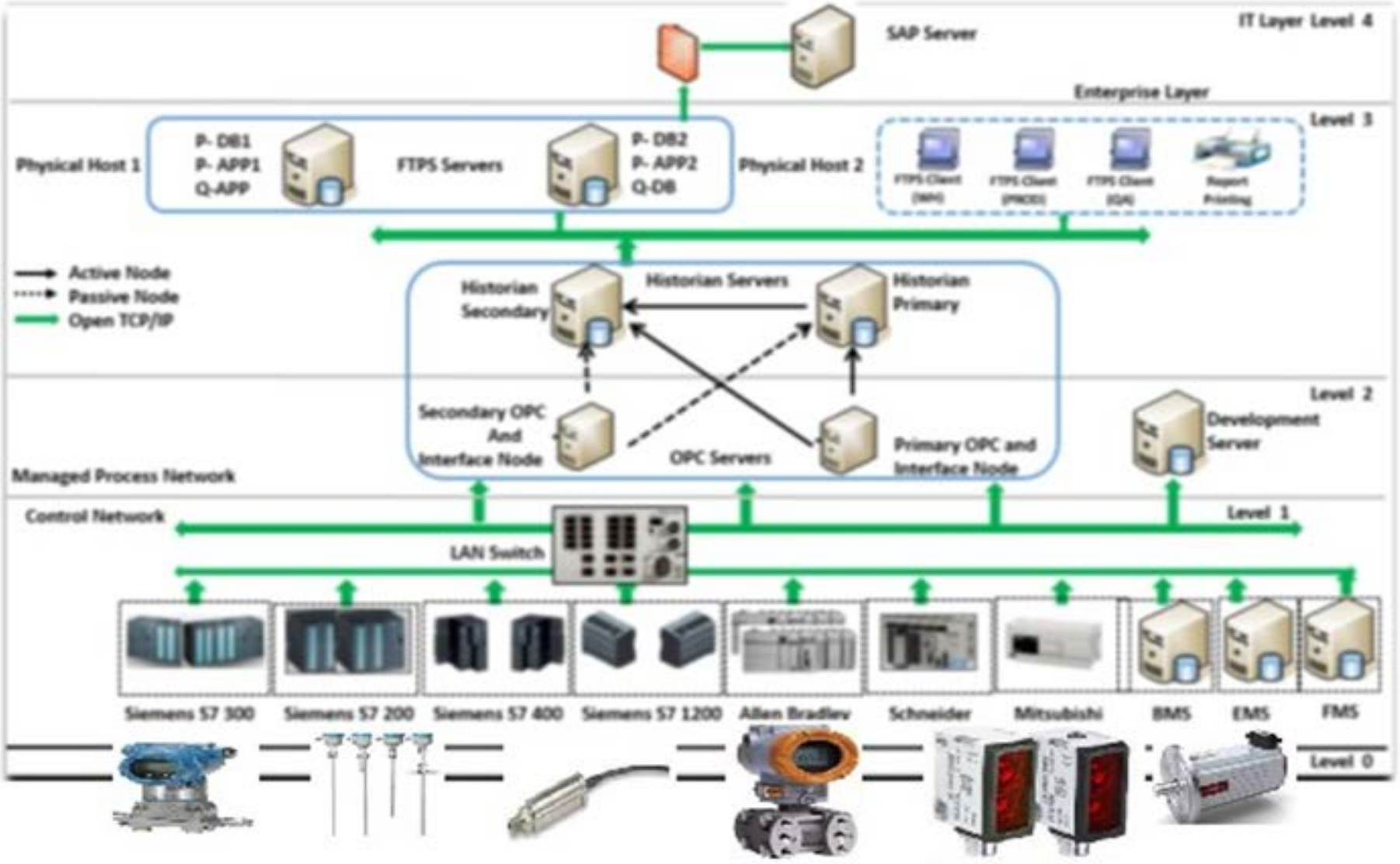
Upon adherence MES send the data to eBMR and once data is stamped can not be altered

Batch End

Additional Features:

- At various stage of manufacturing, MES has provision for sampling along with sample ID to identify sample in LIMS through MES-LIMS interface
- All excursion during batch process are available to review for QA at one place
- MES gets sample result from LIMS through MES-LIMS interface
- When all excursion are closed and LIMS result is satisfactory, MES post the finish goods to SAP for further Release of batch

ARCHITECTURE




Do you
have any
question ?