GMP Laboratory Compliance and Case Studies of Observations at Contract Laboratories

Sunil DeSouza, M.S. CQA
Sr. R&D Quality Officer, AbbVie
Irvine, CA
sunil.desouza@abbvie.com

50 mins: Presentation
10 min: Q&A

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Abstract: A strong analytical laboratory compliance program can be the difference between a smooth drug approval or the start of a long unpleasant road which can includes 483's, tedious corrective actions, frequent re-inspections, delayed/loss of product approvals, criminal investigations and even a consent decree.

For a firm to have a robust compliance program, it must have executive management support and a comprehensive quality management system which, in part, includes a quality monitoring system, regular audit schedule, CAPA planning, a robust training program and an all-round GMP mindset by its employees.

Food and Drug Administration (FDA) and other federal agencies considers laboratory controls to be vital to the safety, quality, and efficacy of drug products. The GMP laboratory is critical in developing, manufacturing and testing drug products and performing investigations for out-of-specification results.

Many firms use Contract Manufacturing Organizations (CMOs) and Clinical Research Organizations (CROs) to improve efficiency and increase productivity. While this can be a great advantage to a firm, if not managed properly this could lead to issues and delays. We will discuss some case studies and examples of incidences at CMO/CRO's in this presentation.

Biography: After completing his B.S. degree in chemistry in India, Sunil received his Masters Degree in Analytical Chemistry at Arizona State University, Tempe. He has previously worked at Teva, B. Braun and currently at AbbVie (Previously Allergan) as an analytical scientist and more recently in a quality role supporting the laboratories. He has a Certified Quality Auditor (CQA) certification and performs internal and external GMP audits.
He has been a Judge in the Chemistry Division for the California Science and Engg. Fair (CSEF) 2016-2021. He has guest lectured on Pharmaceutical Systems at Cal State (Fullerton and San Diego). He enjoys sports and travel.

Analytical Laboratory Compliance

Source:
Laboratory Compliance

DEFINITION

Laboratory compliance refers to procedures, policies and the general approach required in a laboratory to guarantee the analytical results generated are accurate, convincing and appropriate for the decisions which will be made from the data.

Analytical Laboratory Compliance

(Code of Federal Regulations-CFR)

21 CFR Part 210-211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. Part 210 outlines minimum Good Manufacturing Practices (GMP) in manufacturing, processing, packing or holding of all drugs or medicated articles under the purview of the FDA

   Link: 21 CFR Part 210

   § 210.1 - Status of current good manufacturing practice regulations.

   § 210.2 - Applicability of current good manufacturing practice regulations.

   § 210.3 - Definitions.

2. Part 211 refers specifically to the GMP requirements of finished pharmaceuticals.

Analytical Laboratory Compliance

(Code of Federal Regulations-CFR)

Link: 21 CFR Part 211

21 CFR Part 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Subpart A - General Provisions (§§ 211.1 - 211.3)

Subpart B - Organization and Personnel (§§ 211.22 - 211.34)

Subpart C - Buildings and Facilities (§§ 211.42 - 211.58)

Subpart D - Equipment (§§ 211.63 - 211.72)

Subpart E - Control of Components and Drug Product Containers and Closures (§§ 211.80 - 211.94)

Subpart F - Production and Process Controls (§§ 211.100 - 211.115)

Subpart G - Packaging and Labeling Control (§§ 211.122 - 211.137)

Subpart H - Holding and Distribution (§§ 211.142 - 211.150)

Subpart I - Laboratory Controls (§§ 211.160 - 211.176)

Subpart J - Records and Reports (§§ 211.180 - 211.198)

Subpart K - Returned and Salvaged Drug Products (§§ 211.204 - 211.208)

Analytical Laboratory Compliance

Source:
https://en.wikipedia.org/wiki/International_Council_for_Harmonisation_of_Technical_Requirements_for_Pharmaceuticals_for_Human_Use#Guidelines

ICH.org

International Council for Harmonization - (ICH) Guidelines

Q1A-Q1F – Stability

Q2(R1)(R2) – Analytical Validation

Q3A-Q3E – Impurities

Q4A-Q4B – Pharmacopeias

Q5A-Q5E – Biotechnological Products

Q6A-Q6B – Specifications

Q7 – Good Manufacturing Practices

Q8 – Pharmaceutical Development

Q9 – Quality Risk Management

Q10 – Pharmaceutical Quality System

Q11 – Development and Manuf. of Drug Substances

Q12 – Lifecycle Management

Q13 – Continuous Manuf. of Drug Substances and Products

Q14 – Analytical Procedure Development

Analytical Laboratory Compliance

What is the difference between ICH and CFR

The ICH guideline published May 9, 1997 in the Federal Register and has been adopted as guidance in the US. US regulatory requirements (FDA regulations) **must be met for studies conducted in the US**.

For **studies conducted outside for the US in ICH regions** compliance with ICH E6 ensures that the studies will be accepted for review by the FDA as non-US , non-IND studies (per FDA regulation for accepting non-US non-IND studies)

Link to details: Differences between ICH and CFR

Analytical Laboratory Compliance

World Health Organization

WHO – World Health Organization

1. Stability Guidelines

Storage conditions (Climate Zone III/IV)

Climate zone III: Hot dry (30C/35%RH)

Climate zone IVa: Hot humid (30C/65%RH)

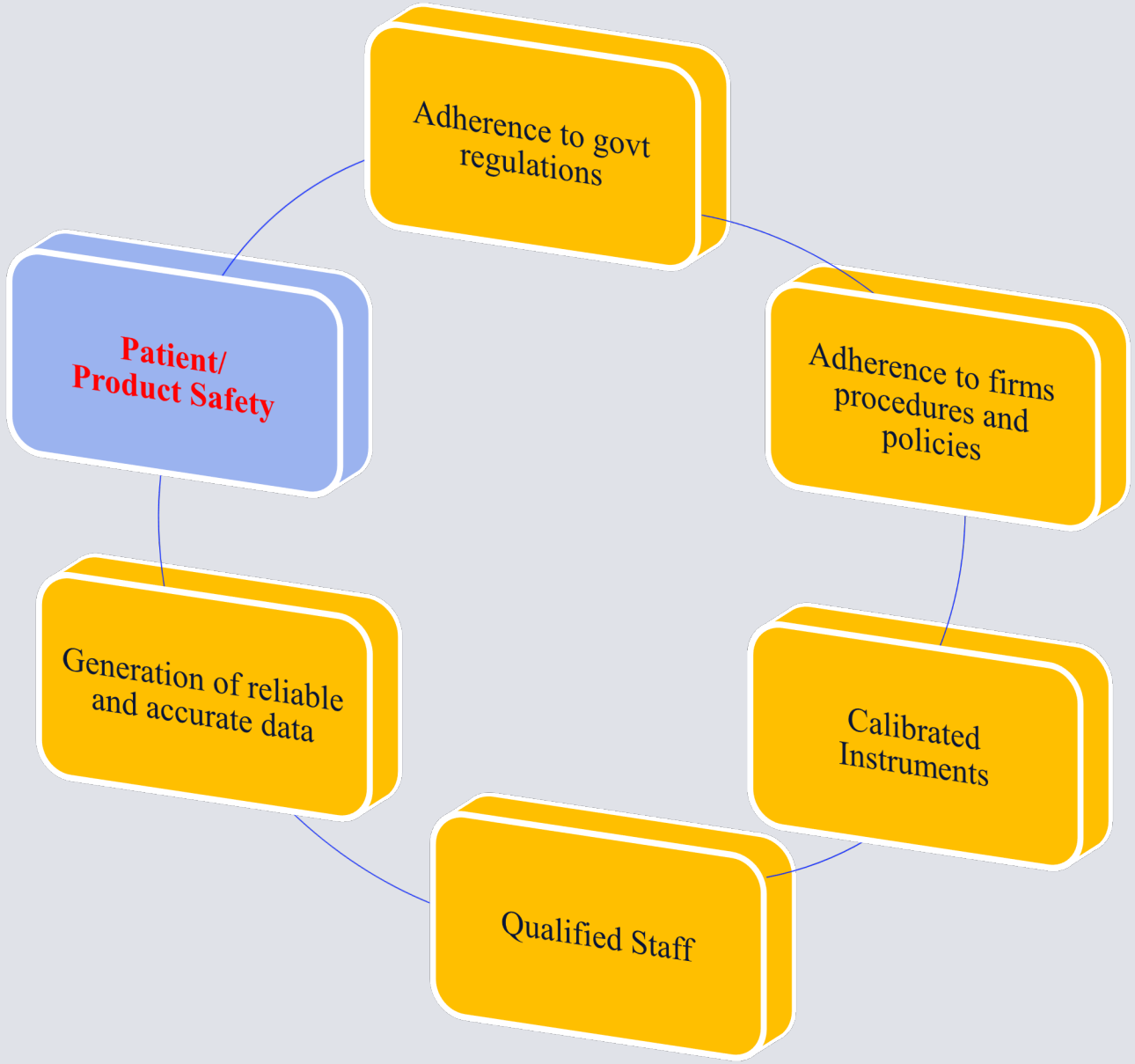
Climate zone IVb: Hot humid (30C/75%RH)-pg 5

2. Good Pharmacopoeial Practices

3. Good Practices for Pharmaceutical Quality Control Labs

4. Good Chromatography Practices

Requirements for a Compliant Analytical Laboratory



Aspects of Analytical Laboratory Compliance (Internal and CRO)

Analytical Instrument qualification and calibration	**Equipment qualification and calibration**	**21 CFR Part 11 compliant software systems (Instrument and Equip)**
Facilities/ Environmental monitoring	**Corporate Procedures and Policies aligned with Federal laws**	**Periodic Review/Update of firms SOP's**
Periodic audits of internal/CRO laboratories	**Investigations OOS, OOT, NC, Deviations, Change Controls (Trackwise®)**	**Validation of Analytical Methods (Non-Compendial & Compendial)**

Support/defend the validity of the analytical results

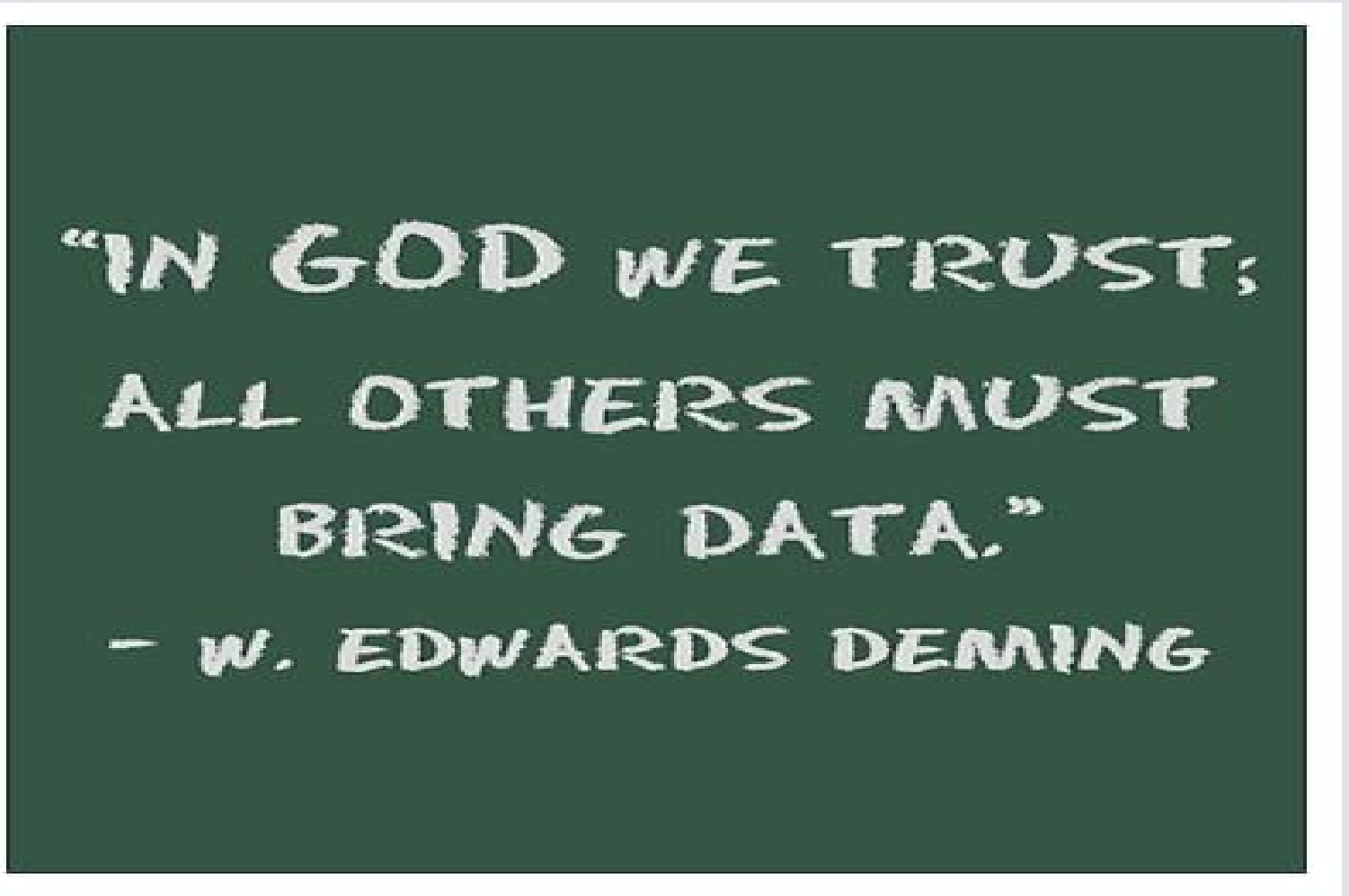
Data Integrity

All important decisions are made using
Reliable Data

- **Dr. William Edwards Deming**

  American engineer, statistician, professor, author, lecturer, and management consultant.

  Developed the sampling techniques still used by the U.S. Department of the Census and the Bureau of Labor Statistics.



Analytical Laboratory Compliance

Instrument qualification and calibration

- Legal requirements (cGMP, CFR, ISO, etc.)
- USP General Chapter <1058> Analytical Instrument Qualification
- Qualification Phases (DQ/IQ/OQ/PQ)
- Manufacturers/Firm's Instrument validation SOP's
- Analytical instrument life-cycle - (Requalification, etc.)

Analytical Laboratory Compliance

Equipment qualification and calibration

- Meets vendors, firms and federal requirements
- Qualification Phases (DQ/IQ/OQ/PQ)
- Custom equipment and software: Global use so must meet all requirements (e.g. **ISO, CE** Mark, etc.)
- Periodic calibration to ensure equipment meets specifications
- Stability Chambers (Temp Mapping)

Analytical Laboratory Compliance

21 CFR Part 11 compliant software applications

- FDA emphasis on data integrity for computerized systems
- Ensures accurate reliable data is generated
- Confidence in instrument operation
- **Audit Trails**
- Agency/Industry standard software Qual (IQ/OQ/PQ)
- Data repository (Lab data, SOP's, GMP docs)
- Data Server Backups (Disaster Recovery)

Reliable data is a critical part of a good drug filing

Aspects of Analytical Laboratory Compliance (Internal and CRO)

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Periodic audits of internal/CRO laboratories	Quality Mgmnt Systems Investigations OOS, OOT, NC, Deviations, Change Controls	Validation of Analytical Methods (Non-Compendial & Compendial)

Support/defend the validity of the analytical results

Data Integrity

Analytical Laboratory Compliance

Facilities/Environmental monitoring (EM)

- Are facilities qualified for handling potent materials
  - Manufacturing (Clean room requirements)
    - ISO-14644 Classification System
      - Microbiology Labs
  - Air Handling/Air Filters (HVAC System)
    - Dust particles, microbial material
      - Gowning

Analytical Laboratory Compliance

Policies and Procedures Comply with Federal laws

- 21 CFR Part 210, 211 – cGMP (Federal Regulation)
- Corporate Policies (analytical, quality, OOS, data integrity, audits)
- Standard Operating Procedures (SOP): Contains operational details in a lab, manufacturing, etc.
- Periodic Review/Update of Policies/SOP's

Analytical Laboratory Compliance

Periodic Review of Firms SOP's

- Well written procedures/SOP
- Aligned with Federal and firms guidelines
- Good e-document tracking system
- Periodic review of SOP's

Analytical Laboratory Compliance

Internal and CRO/CMO Audits

- CRO Audit: Initial/On a Routine Bases as defined (e.g. Biennial/every 2 years Performed by the Audit/R&D/Quality Group)
- Technical assessments (Remote or On –Site)
- Why do we need a CRO: Capabilities, Capacity, Instrumentation.
- Internal Audits: Every 2 years: Performed by the Audit /Quality Group

Analytical Laboratory Compliance

Quality Management System

- eSystem to track OOS, OOT, NC, Deviations, Change Controls
- Key to accurate documentation
- Proper signatories for oversight/investigation
- A sound CAPA plan
- Avoid reoccurrences
- Allows for accurate tracking
- Always prepared for the next audit
- Employee training

Analytical Laboratory Compliance

Validation of Analytical Methods

(Non-Compendial & Compendial)

- Follow firms Method Valid SOP-Non-Compendial
(in compliance with Federal guidelines)
- ICH Q2 (R1)
- FDA/CDER/CBER Guidance for Industry, Analytical Procedures and Method Validation for Drugs and Biologics, July 2015
- Compendial Method Verification-USP <1226> (Selective)
- Stability Indicating
- Acceptance criteria must focus on product safety/efficacy
(Label Claim, Impurity profiles, Trends, Shelf life, Statistical plots)
- Must elicit reliable and meaningful data

Analytical Laboratory Compliance

Source:
Data Integrity
Data Integrity & Compliance- FDA

Data Integrity

- **Data integrity** is absolutely critical in the **pharmaceutical industry** to make sure that the end product meet all the required quality standards. Essentially, it is a process of maintenance and assurance of accuracy and **consistency** of the **data** over its entire life cycle
- **Data integrity risks:**
  - Human Error: Individuals enter information incorrectly, duplicate or delete data
  - Transfer Errors: When data can't successfully transfer from one location in a database to another
  - Bugs and Virus: Viruses software that can invade a computer and alter data / **Hackers**
  - Compromised Hardware: Sudden computer or server crashes
- **Types of Data Integrity**:
  - a) Physical b) Logical c) Entity d) Referential e) Domain f) User-Defined

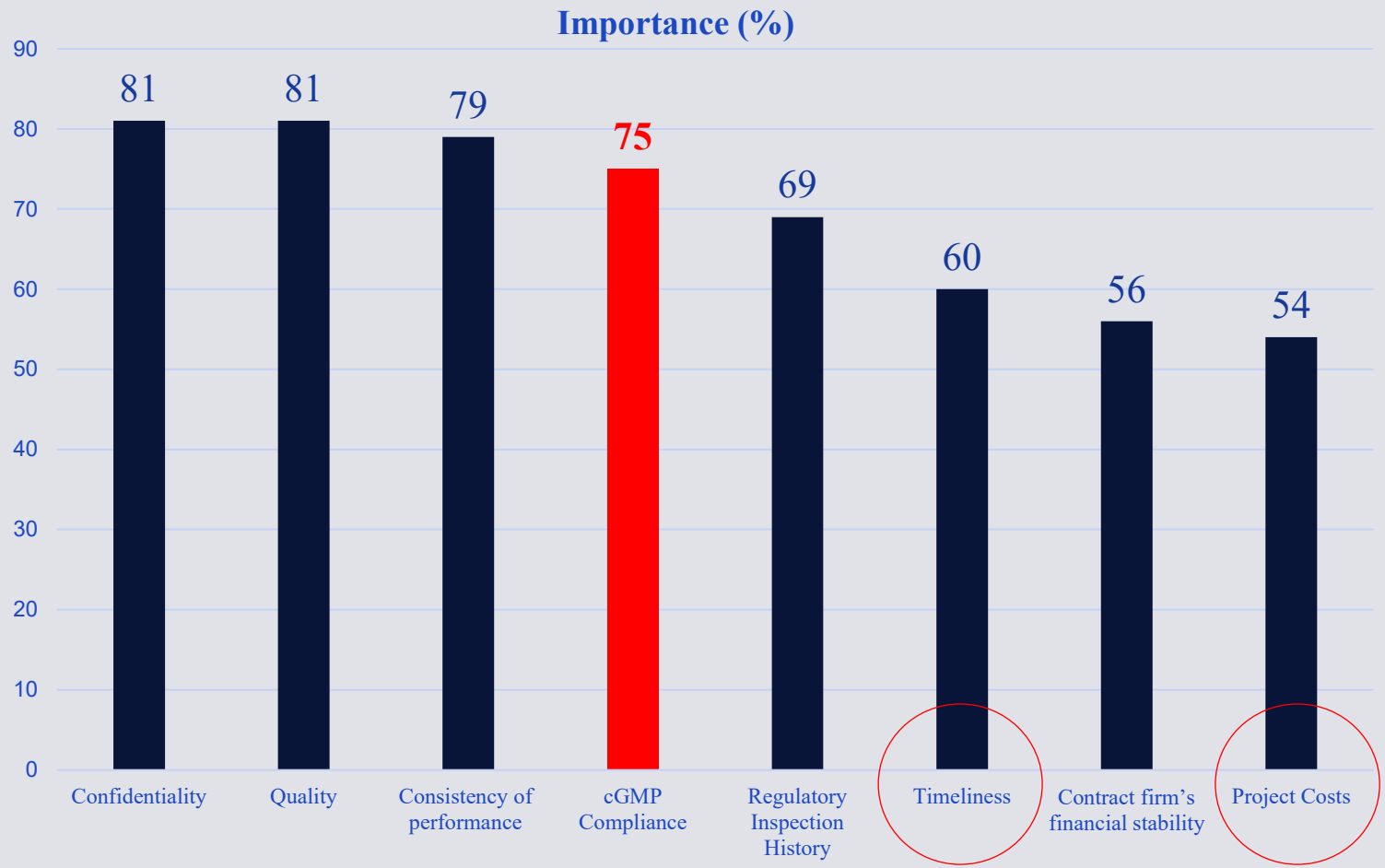
Use of Contract Laboratories

1. Selection Criteria
2. Benefits
3. Concerns
4. Case Studies/Examples

Selection Criteria (CRO)

- Confidentiality (81%);
- Quality (81%);
- Consistency of performance (79%);
- cGMP compliance (75%);
- Regulatory inspection history (69%);
- Timeliness (60%);
- Contract firm's financial stability (56%); and
- Project cost (54%).

Source:
What to Look for in Selecting a CRO/CMO



Contract Laboratories

Expectation from a CRO

- cGMP (Comply with Federal guidelines)
  - Maintain Confidentiality of Intellectual Property
  - Instrumentation/Equipment
  - Good Documentation
  - Procedures and SOP's
  - Software/Audit trails /Data Integrity & Security
  - Capabilities (Chem, Micro, biologics, stability chambers, etc.)
  - Accommodating to the firm's needs
- Technical Assessment/Audits

Benefits of using CRO's

- Well trained staff
- Workload overflow, tight timelines, High throughput
- Offers comprehensive services (Instrumentation, Development, Validation, Leachables and extractables, Stability, QC, Microbiology)
- Can accommodate complex scheduling/testing requirements
- Multiple capabilities (micro/chemistry, stability chambers, etc.)
- Good Change Management system (Change Controls)
- Proficiency with running specialized analytical equipment (ICP-MS, NMR, MS, etc.)
- Multiple convenient geographical locations (PPD, Eurofins)-Within the US and worldwide
- Seamless operations, follow standardized/current GMP policies
- Audited and approved by Federal agencies
- Ease of method transfers to different locations
- Reputation for doing good GMP work. On time delivery. Competent Technical staff

Concerns/Challenges with using CRO's

- Source:

Concerns/Challenges with using a CRO/CMO

- High turnover of personnel
- High testing volume
- Instrumentation: Older, compatibility issues, impacts method transfers, etc.
- Software Compatibility
- Limited in-house supervisorial/technical support
- Inexperienced analysts
- Lack of thorough investigations
- Inadequate GMP documentation
- Projects range from simple to complex and sometimes a different cGMP standard is applied
- Purchase of new business (risk)
- Language/Comprehension
- **Case studies/examples later**

Concerns/Challenges with using CRO's
(Contd….)

Six critical areas which pose challenges for regulatory labs

- recruitment and retention of staff
- staff development
- capital budgets for equipment purchase
- operating budgets
- facility infrastructure, and
- management of change (i.e. change controls).

Cost of Non-Compliance

Source:
[Cost Of Non-Compliance]

- Invalid/Unreliable Data
- Delay/denied drug approval
- Loss in revenue (no drug sales)
- Additional filing fees with the agencies
- Corrective action
- Use of consultants
- Closure of facilities
- Loss of reputation
- Consent decree

Examples/ Case Studies (CRO)

INTERACTIVE with the audience

I will take your comments/questions **at the end** of the presentation.

Please remember the slide number for reference.

If anyone has an important case study to discuss we can do that with any leftover time.

Examples

OOS/Deviations Investigations

Physical Appearance Specs: White to Pink powder

Result: Off-White

- CRO thinks result is a pass. (within the scope of color range)
- Firm says its OOS

Outcome: Firm not informed in a timely manner of this result.

CAPA: Investigation, OOS documentation, retraining

Examples

Reference Standard Use

Incident: QC site ran out of Ref Std material during validation. Additional **Unqualified** Ref Std was sent from CRO R&D Site to QC site to complete validation

Outcome: Unqualified Ref Std was used for Validation work. Delays

CAPA: Investigation and Non-Conformance was required. Risk assessment, Memo justifying use of Ref Std was retroactively written

Examples

Out-of-Specification Intimation to Firm

Incident: CRO did not inform firm about failure/OOS during method validation within 2 business days

- The quality agreement (QA) is not explicit about 2 business days for lab related failures. QA focusses mainly to manufacturing related issues.

Outcome: Back and forth (Delays)

CAPA: Update QA for accuracy, Include 2 business day requirement in testing protocol

Examples

E-Document Signoff

Requirement - Validated document signing software.

Firm wants to be the last signatory on the GMP document

Outcome:

- Absence of e-signature software at CRO
- Incompatible doc-signing software
- Procedural differences at Firm and CRO
- Doc-signing software access, training
- Legalities
- Signed document repository (Firm or CRO)

CAPA:

- CRO signs document and sends to firm for final signatures
- Firm/CRO-Allows access to e-doc software platform
- Wet-Sign signature page and scan into final document

Examples

Stability Sample Labelling at CMO

Incident: CMO added unqualified labels to stability samples.

Outcome

- Potential leachables show up that are not legitimate and should be excluded.
- Stability study compromised?

CAPA:

- Memo to document the occurrence, corrective action and detail potential risk to the stability study
- Additional work required to invalidate these leachable(s) due to CRO labelling

Examples

Development Work at CRO

Incident: CRO did limited development work for a method validation. (Ruggedness, Robustness was not performed)

Outcome: Issues with impurity peak profile, purity, baseline noise, reagent grades, 2nd column consistency

CAPA: Expand development work at CRO (as necessary), Firm must review all development data, Firms analytical staff to have technical discussions with CRO, review method nuances with CRO

Examples

Multilingual Technical GMP documents

Incident: Bilingual protocol was not accurately translated from foreign language to English resulting in some misunderstanding by the analyst reading the English translation.

Outcome: Caused some analytical errors due to inaccurate interpretation, Delays

CAPA Suggestion: - Templates in each language for each method would reduce the translational errors. Reviewed by a SME

Examples

Significant Figures

Incident: Insufficient significant figures reported in valid report. Did not match specifications

Outcome: Delays in product release due to mismatch in results vs specifications

CAPA: Include details for significant figures in test protocol.

Examples

Covid-19 (Johnson and Johnson and AstraZeneca)-March 31, 2021

Incident 1: J&J CRO (Emergent Biosolutions): Observation was low level mold and yeast isolates, cracked vials, poor training.
Incident 2: AstraZeneca CRO (Emergent Biosolution): mistakenly mixed the ingredients

Outcome J&J: Batch rejected, Delays, Costs, Patient impact, Reputation.

Outcome AZ: 15 million doses destroyed, Patient impact, Reputation.
AstraZeneca kicked out of US

CAPA: Improve Quality management system, Sr. management involvement, employee training program, Audits, Investigate root cause and CAPA for the FDA observations.

Examples (UPDATE)

Covid-19 (Johnson and Johnson)-May 14, 2021

Incident 1: J&J CRO (Emergent Biosolutions): Observation was low level mold and yeast isolates, cracked vials, poor training.

Outcome J&J: Batch rejected, Delays, Costs, Patient impact, Reputation.

CAPA: Responded to FDA findings with commitments that meet/exceed the FDA's standards

News Release (May 12)
News Release (April 29, 2021)

General CAPA's for the Above Observations

- Create **database of observations/issues**
- **Technical assessments** to cover prior issues/concerns
- Have **regular conversations** with the CRO labs with a clear agenda
- Involve **SME** in these meetings
- Write **thorough testing protocols**. Include important details
- Discuss issues/concerns & corrective actions and include in future conversations
- Regular risk mitigation discussions with sr. management to prevent reoccurrence
- **After every project with a CRO, we keep a list of what can be improved for the future**

Final Thoughts

- Compliance: Critical component to a successful/profitable operation
- Senior Management MUST be supportive of compliance/GMP
- Ethics Dept/Officer: Confidential reporting, No retaliation
- Very strong training program. GMP mindset
- Period Audits/Strong CAPA program
- Good GMP documentation
- Constant improvement. Best Practices, Lessons Learnt
- Quality Oversight: Uncompromised, Free of Influences
- "No right way to do a wrong thing"

Audience Feedback

In the remaining time we have left:

I would like to hear from the audience about a specific situation with a CRO or a firm and how they were able to resolve it.

Contact info: sunildesouza@gmail.com