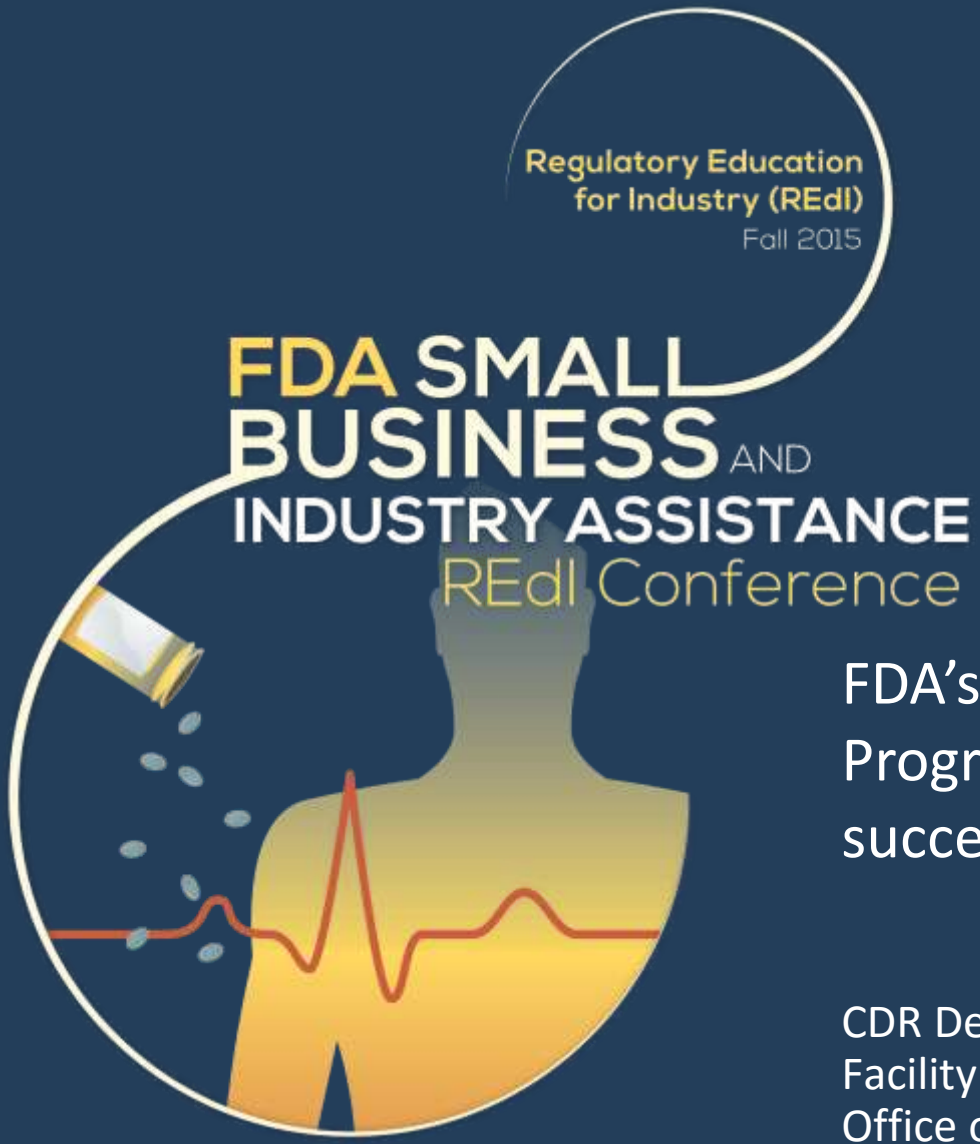

FDA's Pre-Approval Inspection (PAI) Program and How to prepare for a successful outcome

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Overview

- FDA's Pre-Approval Inspection (PAI) Process
- Practical tips for a successful outcome
- Case Studies/Proactive Takeaways
- Questions

PRE-APPROVAL INSPECTION COMPLIANCE PROGRAM 7346.832

Pre-Approval Inspection Compliance Program 7346.832, Rev. 4, eff. 5/12/2010

The Food, Drug, and Cosmetic Act provides that FDA may approve an NDA or an ANDA only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity.

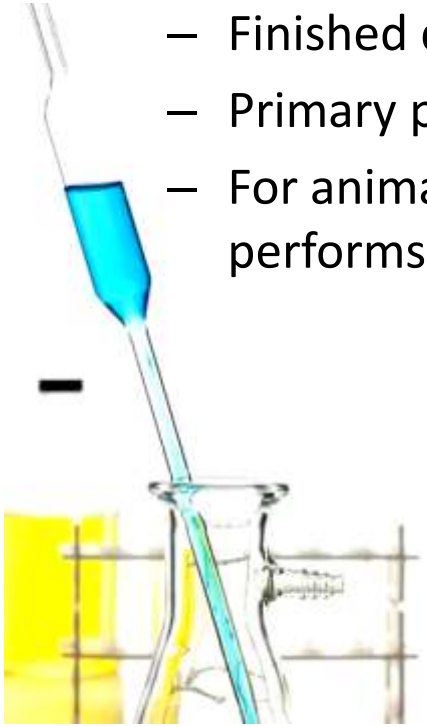
§§ 505(d) and 505(j)(4)(A) ***(21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))***

Site Evaluation

Before approval, FDA evaluates the establishments by on-site inspections and/or by establishment file review when the firm is named in the Chemistry, Manufacturing, and Controls (CMC) section of a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or Biologic License Application (BLA)

Which sites generally trigger a facility evaluation for a pre-approval inspection?

- Facility evaluations are conducted for:
  - Finished dosage manufacturers
  - API manufacturers
  - Finished dosage and API testing sites
  - Primary packaging and labeling sites
  - For animal derived APIs, the facility that performs the crude extraction



FDA generally does not evaluate the following sites for a pre-approval inspection

☑ Intermediate manufacturers

- On a **case-by-case** basis; evaluated only if the intermediate is consider critical to quality of the drug product.

☒ Exhibit batch manufacturers (if not proposed commercial site)

- Note: The site could be added on a for-cause basis if the review identifies concerns

☒ Component manufacturers

- Includes syringe, vial, or stopper manufacturers and component-only sterilization sites
- OPF/DIA generally **does not** evaluate these sites unless for-cause basis
- It is the drug product manufacturer's responsibility to qualify their suppliers.

☒ Excipient manufacturers

- OPF/DIA generally **does not** evaluate these sites, unless it is a novel excipient and/or the excipient manufacturing process is considered a critical step in the overall drug manufacturing process.

☒ Secondary packager/labeler

- OPF/DIA generally **does not** evaluate these sites

*note all above sites are required to meet the statutory CGMPs per FD&C Act and may be routinely inspected if registered as a drug manufacturer

When does FDA perform PAIs?

Use risk based Priority Inspection Criteria to make the decision based on the following risks:

- Facility Risk
- Product Risk
- Process Risk

When does FDA perform PAIs?

Facility Risk

- CGMP issues relevant to application product
- Recent FARs relevant to application product
- Recent recalls relevant to application product
- Numerous applications filed at once

When does FDA perform PAIs?

Product Risk

- New molecular entity
- First application filed by applicant
- First ANDA filed for an approved drug
- RLD has complaints, ADEs, stability issues
- Patient population or for serious condition
- Breakthrough therapy, shortage situation

When does FDA perform PAIs?

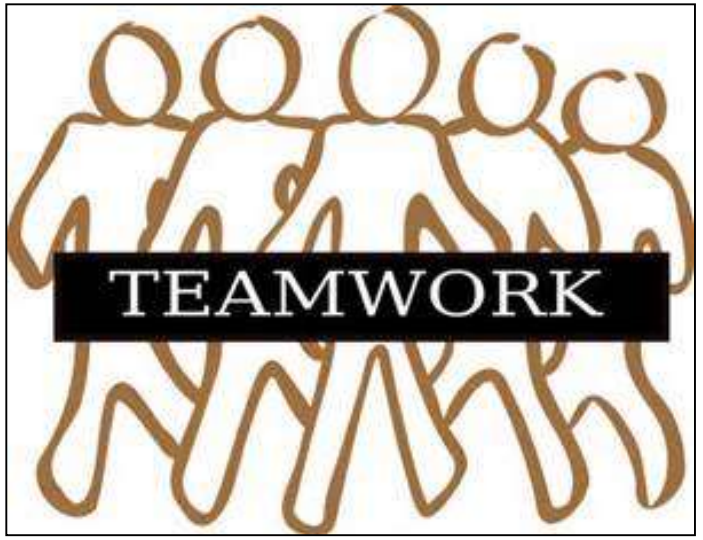
Process Risk

- Narrow therapeutic range (95%-105%)
- API derivation is high risk (derived from animal tissue)
- PAT, NIR, QbD
- Development data is incomplete
- Batch records non-specific
- Complicated process
- Substantially different process than previously covered at facility

The Pre-Approval Inspection team

If an inspection is determined to be needed FDA will send a team of individuals to conduct the pre-approval inspection. The team may include:

- Investigators
- Other Specialists
  - Chemistry Expert
  - Microbiology Expert
  - Process/Facility Expert
  - Formulation Expert



Pre-Approval Inspection Program (7346.832)

2.1 SCOPE

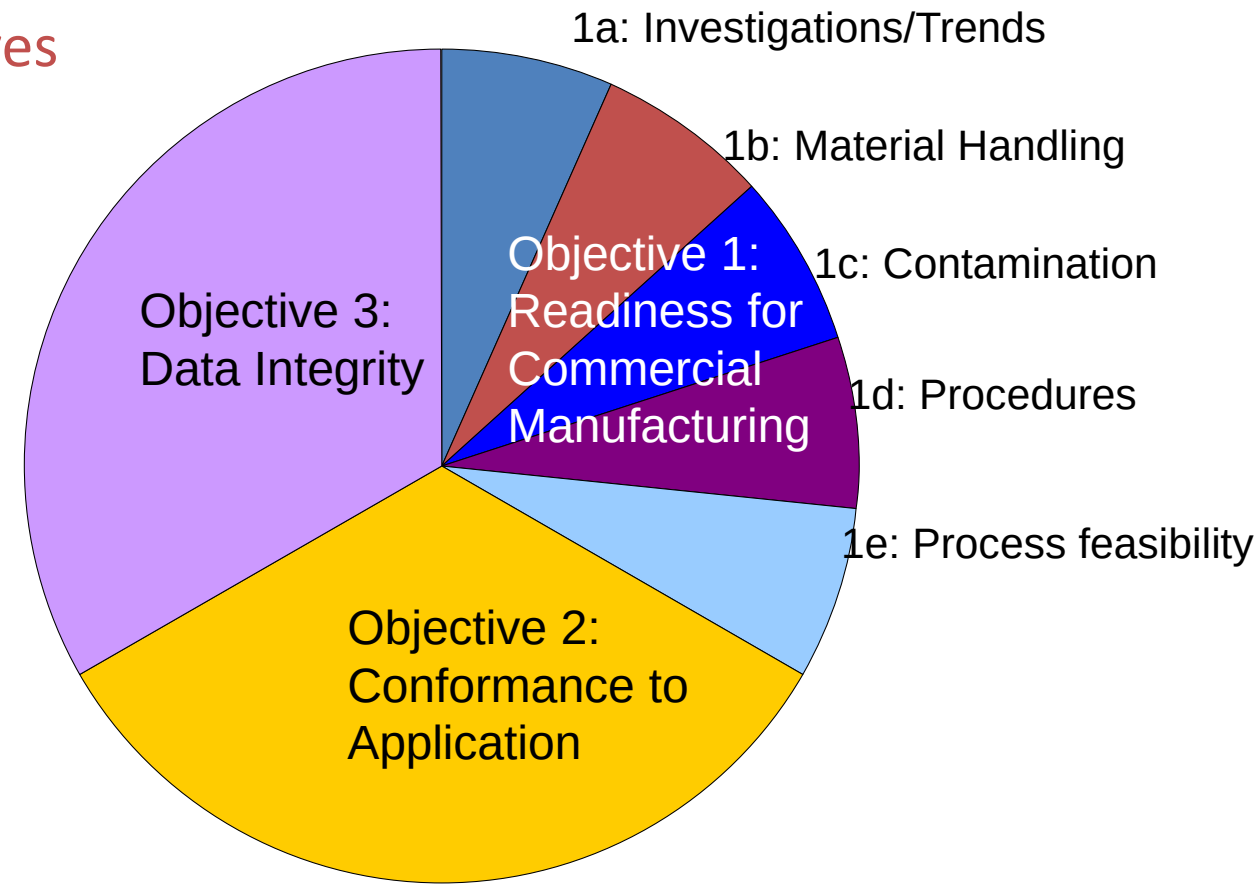
A pre-approval inspection (PAI) is performed to contribute to FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.

PAI is product specific

- Limited or no commercial manufacturing
- More focus on development data
- More emphasis on authenticity of data and application commitments
- Process validation commonly not completed
- Application actions are administrative; typical enforcement used for marketed products do not apply
- Trend toward more experts involved in the inspection

Pre-Approval Inspection Program (7346.832)

PAI Objectives (Sections 3.3-3.4)



PAI Coverage: Objectives

Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the biobatch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Objective 3: Data Integrity Audit

Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate.

PAI Outcomes

The inspection is one part of the approval process.

Lead investigator will make a recommendation at the conclusion of the inspection:

Recommend Approval

- Indicates that the inspection found no significant issues
- Response to observations is important

Recommend Withholding of Approval

- Investigators observed that the site is not GMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete.
- Response to observations is **critical**

CDER's Office of New Drugs or Office of Generic Drugs makes the ultimate decision on whether to approve or withhold approval of the application or licensure.

PRACTICAL TIPS FOR A SUCCESSFUL PAI OUTCOME

Be Prepared For the PAI

Once an application is submitted to the Center, the firm and all facilities mentioned are considered by FDA to be ready for inspection.

The inspection team will determine if:

- The site is ready for commercial manufacturing
- The information submitted is consistent with site records
- The information submitted is complete and accurate

Readiness for Commercial Manufacture

The investigative team will determine whether your firm has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

- Evaluate overall CGMP compliance as it relates to the application product
- Evaluate the specific PAI product and process
  - ✓ Is the facility adequate/qualified-building; equipment; water systems?
  - ✓ Is there evidence/data to support the manufacturing process and specifications?
  - ✓ Will review development data for all R&D batches
  - ✓ Will review Product Development Report
- Will review batch records for submission batches (pivotal, qualification and/or biobatches)
- Focus on change control, deviations and trends relating to the development process to determine that there is adequate evaluation

Readiness for Commercial Manufacture

- Will evaluate sampling plans; testing of components and product
- High focus on your supplier qualification program
- Evaluate facility and equipment procedures with a focus on contamination controls
- Evaluate the quality system specifically for batch release, discrepancy management, investigation completeness, complaint and ADE handling.
- Focus on laboratory system (SOPs; Personnel; Training) and stability data
- Evaluate test methods (validated?) and impurity profile

Conformance to Application

The investigators will verify that the formulation, manufacturing and/or processing methods, and analytical methods are consistent with descriptions contained in the CMC section of the application.

As part of the inspection, they will audit records, equipment, procedures, and the batch records submitted in the application as well as inspect the manufacturing equipment and facility to assure:

That the proposed production process is the same process that was used for the manufacture of the bio/stability batches (and other pivotal clinical batches).

Conformance to Application

Investigators will verify the following:

- Observe manufacturing operations and equipment to assure they are consistent with those described in the application
- Review on-site analytical methods to assure they are consistent with those filed in the application
- Will assure that stability samples are stored under the conditions described in the stability protocol filed with the application

Conformance to Application

Investigators will compare stability lots and testing conditions at the site versus what is listed in the application

Investigators will visit stability chambers to verify:

- Correct packaging configuration
- Correct orientation
- Audit recording charts during time period
- Alarm logs
- Correct temp and humidity conditions

Data Integrity

<u>The investigators will audit the raw data</u>

To authenticate and verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section of the application such that CDER product reviewers can rely on the submitted data as complete and accurate.

Data Integrity

Does the data have factual integrity?

- Data is accurately submitted in the application
- Chromatogram directly calculates to summary

Does the data have contextual integrity?

- Data is supported by additional information observed at the firm
- Missing records
- Unexplained losses of inventory of components

Data Integrity

- Investigators review raw data used to generate results
- Control/security of raw data
- Audit for authenticity and accuracy
  - Review raw data for biobatch and stability batch(es), including laboratory testing and manufacturing
  - Inventory records/equipment logs
  - Passing data submitted instead of failing data
  - Improper invalidation of OOS results which were then not submitted
  - Exclusion of specific lots from the stability program to avoid submitting failing results

Data Integrity

FDA will take action against companies that commit data fraud or provide false information to the agency.

"Companies must provide truthful and accurate information in their marketing applications…. The American public expects and deserves no less."

Janet Woodcock, M.D., Director, CDER

February 25, 2009 FDA News Release

FDA's Application Integrity Policy

U.S. Department of Health & Human Services www.hhs.gov

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FDA Takes New Regulatory Action Against Ranbaxy's Paonta Sahib Plant in India

Agency halts review of drug applications from plant due to evidence of falsified data; invokes Application Integrity Policy

The U.S. Food and Drug Administration today announced that a facility owned by India-based Ranbaxy Laboratories falsified data and test results in approved and pending drug applications. The facility, Paonta Sahib, has been under an FDA Import Alert since September 2008.

The FDA is continuing to investigate this matter to ensure the safety and efficacy of marketed drugs associated with Ranbaxy's Paonta Sahib site. To date, the FDA has no evidence that these drugs do not meet their quality specifications and has not identified any health risks associated with currently marketed Ranbaxy products.

In the meantime, the FDA recommends that patients not disrupt their drug therapy because this could jeopardize their health. Individuals who are concerned about their medications should talk with their health care professional.

The affected applications are for drugs that fall into three categories:

- Approved drugs made at the Paonta Sahib site for the U.S. market;
- Drugs pending approval at the FDA that are not yet marketed; and
- Certain drugs manufactured in the United States that relied on data from the Paonta Sahib facility.

Companies must provide truthful and accurate information in their marketing applications, said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER). The American public expects and deserves no less.

To address the falsified data, the FDA has invoked its Application Integrity Policy (AIP) against the Paonta Sahib facility. The AIP is invoked when a company's actions raise significant questions about the integrity of data in drug applications. This AIP covers applications that rely on data generated by the Paonta Sahib facility only.

Under the AIP, the FDA has asked Ranbaxy to cooperate with the agency to resolve the questions of data integrity and reliability.

Local intranet 100%

Product Specific findings and deficiencies that should result in a district recommendation to withhold approval

- ✓ Significant data integrity problems including misrepresented data or other conditions related to the submission batch
- ✓ Serious CGMP concerns with the manufacture of a biobatch or demonstration batch, such as a changes to formulation or processing that may cause FDA to question the integrity of the bioequivalence study
- ✓ Significant differences between the process used for pivotal clinical batches and the NDA submission batch
- ✓ Lack of complete manufacturing and control instructions in the master production record or lack of data to support those instructions
- ✓ Lack of capacity to manufacture the drug product or the API (if the firm is not ready for an inspection, the district should request a letter from the establishment)
- ✓ Failure to meet application commitments

Product Specific findings and deficiencies that should result in a district recommendation to withhold approval

- ✓ Full scale process validation studies were attempted prior to the PAI, demonstrate that the process is not under control and establishment is not making appropriate changes
- ✓ For products for which full scale summary information is provided in the application, establishment has not demonstrated that the product can be reliably manufactured at commercial scale and meet its critical quality attributes
- ✓ Incomplete or unsuccessful method validation or verification
- ✓ Records for pivotal clinical or submission batches do not clearly identify equipment or processing parameters used
- ✓ Significant failures related to the stability study that raise questions about the stability of the product or API
- ✓ Failure to report adverse findings or failing test data without appropriate justification

To ensure a successful PAI

Have a proactive compliance approach:

- Firm is aware of significant issues before inspection; CAPAs in place; if needed
- Senior management is aware of compliance / inspection issues at site so there are no surprises during the inspection
- Sponsor conducts due diligence before they name contractors/suppliers in applications and prepares all sites for PAIs
- Quality and Operations work together to investigate deviations/issues…Responsible person for issues identified and accountable
- Quality and Operations work together to best present significant issues during inspections (identify Subject Matter Experts)

To ensure a successful PAI

- Have a development report that compiles documentation that represents a thorough understanding of the application product and process
- The development report adequately serves as the basis for justification of the process to support the filing
- Communicate product and process risks to manufacturing sites and have them reflective in the performance measurements that are collected and monitored during manufacturing to help prevent problems after launch

CASE STUDIES

Case 1: Failure to Report Failing Data

There is no assurance that the finished product will consistently meet its finished product specifications. For example,

- Review of the development batch records revealed that several batches failed dissolution. This data was not reported in the filing submitted to the agency. The investigations conducted into the failures stated that the assignable cause was the wet granulation process, compression of the core tablets, and/or the enteric coating of the core tablets, without further explanation. During the inspection, the firm hypothesized that the root cause was the dew point during the enteric coating step. The firm does not have the capability of controlling the dew point in any of its coaters.

- The firm does not have sufficient control of the tablet press. In a memo, the firm stated "At this point manufacturing operations only operates the press with the presence of the vendor due to the difficulty of optimizing the start up."

Recommendation: Withhold for failure to report adverse findings

Case 1: Failure to Report Failing Data

What happened

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- Different batches would require different tablet press settings, and the firm had no idea why.
- Investigators also found failing dissolution release testing without a root cause identified. This failing data was not reported.
- During the inspection, the firm hypothesized that the root cause for the dissolution failures was the dew point during the enteric coating step. The firm does not have the capability of controlling the dew point in any of its coaters.

Case 1: Failure to Report Failing Data

Takeaways

- Investigate deviations/issues prior to the PAI…Responsible person for issues identified and accountable
- Have SME ready to present significant issues during inspections
- Process design (Stage 1) must be completed and adequate prior to the PAI inspection. Need evidence/data to support the manufacturing process
- Knowledge gained during development should be incorporated into process design/control strategy.
  - ✓ Dissolution failure investigations may result in manufacturing changes depending on the root cause
  - ✓ Manufacturing changes may result in gaining sufficient control of the tablet press

Case 2: Nonconformance to Application

The firm lacks data for the qualification of the proposed container closure system (LDPE bags) to store the finished API ABC. For example, the firm lacks storage stability data. The current stability studies were performed on samples packaged in amber glass bottles. However, the drug substance is packaged in LDPE bags.

Recommendation: Withhold for failure to meet application commitments

Case 2: Nonconformance to Application

What happened

- The drug substance is packaged in LDPE bags; however, the stability studies were conducted in amber glass bottles. The firm had no data to support the qualification of the proposed container closure system (LDPE bags) to store the finished API.

- The firm responded that they will package the API in amber glass bottles until they collect adequate stability data to support packaging in LDPE bags.

Case 2: Nonconformance to Application

Takeaway

Know your commitments and be prepared for the inspection!!

Case 3: Knowledge Management

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. There is no assurance that the product solutions are uniform. For example,

The firm manufactured 10 production size lots of drug product. 9 of 10 batches failed for API X. The draft investigation has identified that due to the small quantity of API X required for each batch … minor drug loss can yield OOS results. The firm manufactured a batch …. to evaluate the method of dispensing API X into a separate flask of excipient y directly after drug weighing to eliminate any non-recoverable loss …This engineering report has not been finalized and the investigation in the 9 failures is still open.

Recommendation: Withhold for unsuccessful scale-up

Case 3: Knowledge Management

What happened

- Firm X purchased drug product solution from Firm Y without the development report or batch record and had no experience with this type of complex formulation. Firm X used current in-house equipment for manufacturing.

- After Firm X experienced problems in scale-up, they contacted Firm Y and found that there were significant differences in their manufacturing process as compared to Firm Y's manufacturing process

- R&D personnel from Firm Y visited Firm X and shared their manufacturing knowledge.

Case 3: Knowledge Management

Takeaway

- Knowledge dissemination not only useful within a company, but beyond as well. Information (product knowledge) should be part of the transfer of the product between companies.
- Communication between companies is key to a successful transfer
- Knowledge gained during scale-up should be incorporated into process design/control strategy. In this case, manufacturing scale-up issues were the root cause.
- Knowledge Management can assist in the preservation of prior knowledge (including between companies) during technology transfer

Questions????

Please complete the session survey:

surveymonkey.com/r/DRG-D2S3