



Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

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CGMP Case Studies

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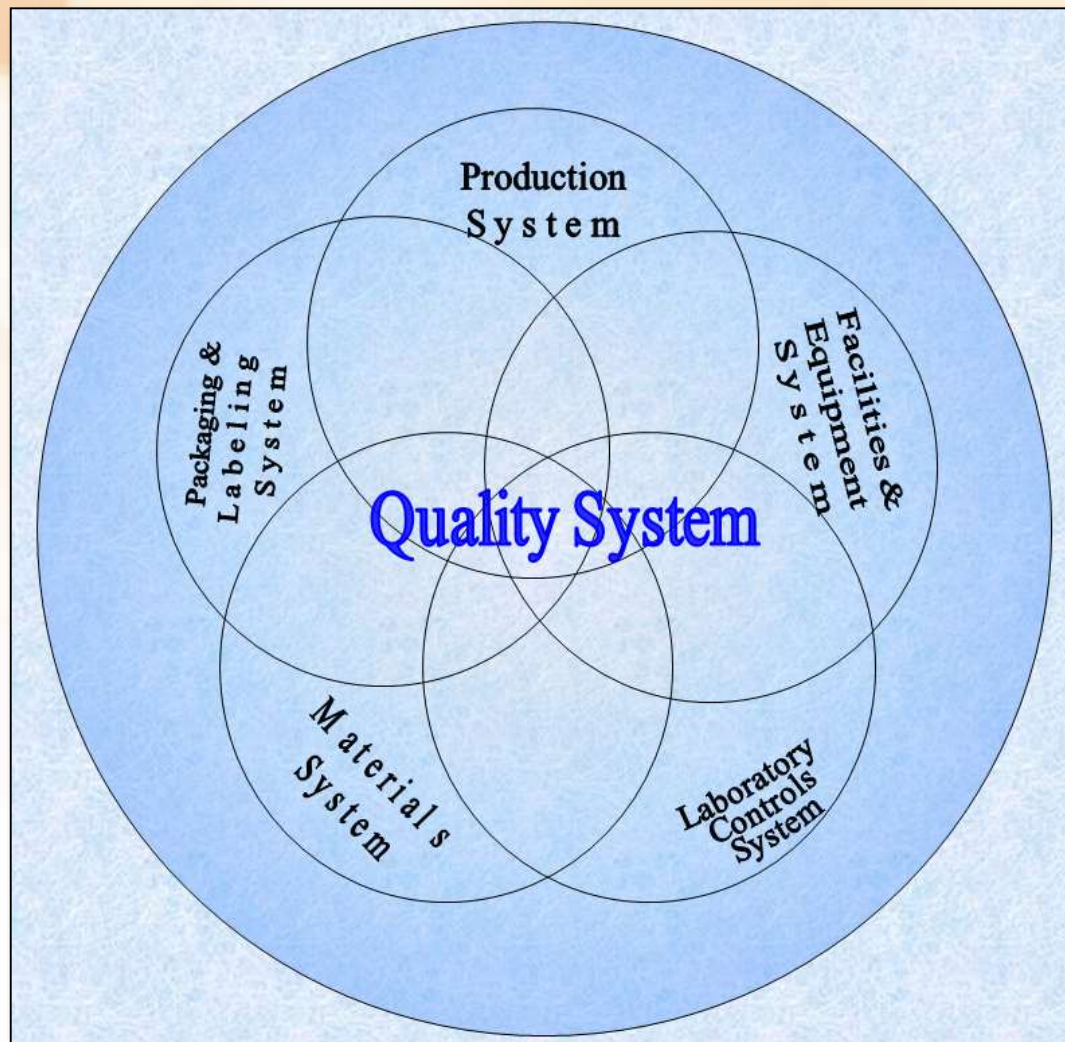
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Compliance Branch 4



The Six Components

- **Quality**
- **Production**
- **Laboratory**
- **Materials**
- **Facilities & Equipment**
- **Packaging & Labeling**





These cases lead to:

- **FDA Form 483 observations**
- **Warning Letters**
- **Recalls**
- **Import Alerts**
- **Regulatory meetings**



Case 1 – Facilities & Equipment System

Background:

- Repackaging beta-lactams in a facility that is not dedicated
- Personnel move freely between beta-lactam and non-beta-lactum manufacturing





Case 1: Facilities & Equipment System

What Happened:

- After discussions with FDA, firm recalled the product.
- Firm ceased manufacturing of beta lactams.
- Firm decontaminated and renovated facility
- FDA issued a Warning Letter



Case 1: Facilities & Equipment System

Takeaways:

- **No safe level of beta lactam contamination. Severe allergenic response can occur when exposed to extremely low levels of beta-lactams.**
- **Cleaning cannot substitute for proper segregation.**
- **Any test intended to detect beta-lactam contamination provides only limited confidence due to analytical method limitations.**
- **Complete segregation is important.**



Case 2 – Packaging & Labeling System

Background:

- Firm repackages therapeutically significant drugs
- Operators are changing the master labels
- No written procedures for manual repackaging
- Complaints of air bubbles and low fill volumes





Case 2: Packaging & Labeling System

What Happened:

- **Firm recalled**
- **FDA issued a Warning Letter citing inadequate manufacturing controls and misbranding violation**



Case 2: Packaging & Labeling System

Takeaways:

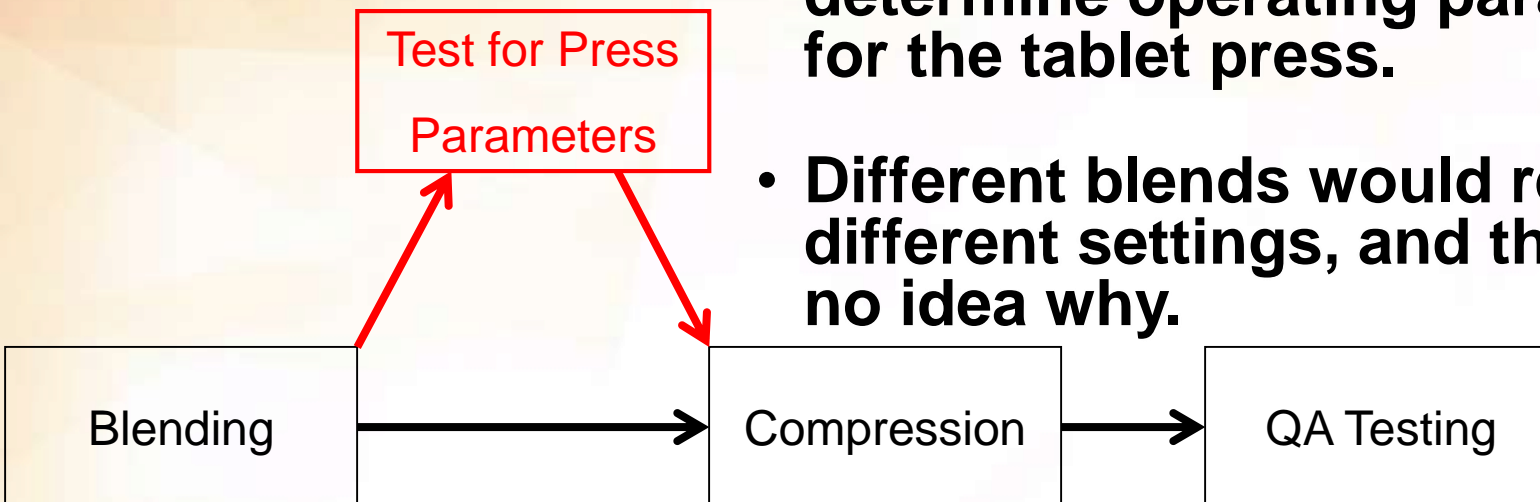
- **When a drug product is repackaged, its characteristics may change that could impact the safety and efficacy.**
- **Improper repackaging of drug products can cause serious adverse events.**
- **A repackager must comply with all applicable sections of 21 CFR Parts 210 and 211.**



Case 3: Production System

Background:

- Firm markets an extended release tablet.
- Production included manufacture of extended release “beads” which were blended with excipients and then compressed.
 - Operations had to pre-compress blend samples in the lab to determine operating parameters for the tablet press.
 - Different blends would require different settings, and the firm had no idea why.





Case 3: Production System

What Happened:

- **During a routine FDA inspection, investigators saw the pre-compression practice.**
- **Investigators also found inadequate release testing, especially in light of known process problems.**
- **Warning Letter issued for lack of process validation.**



Case 3: Production System

Takeaways:

- Operational parameters should be selected using risk-based, science-based approach.
- Process design/qualification (Stage 1-2) must be completed and adequate prior to distribution of your product.
- Knowledge gained during scale-up should be incorporated into process design/control strategy.
- Sampling plans for batch release should be scientifically sound.



Case 4: Laboratory System

Background:

- Firm manufactures multiple transdermal patch products for many years.
- Firm developed a new drug, utilizing the same adhesion matrix as it did for others.
- 1st year on the market – received ~5000 complaints regarding efficacy and difficulty using the patch.
- Up to 25% of the drug was sticking to the liner.



Case 4: Laboratory System

What Happened:

- Firm's investigation indicated a drug/adhesive interaction problem.
- Firm argued that since there were no specifications regarding peel force in their application, a recall wasn't warranted, and it could continue to distribute.
- Firm ultimately recalled.
- FDA issued a Warning Letter citing lack of specifications, as well as a failure to assure proper strength.
- Firm established a peel force specification.



Case 4: Laboratory System

- **CMC review and the CGMP program:**
 - **21 CFR § 211.180(e)**
 - *"Written records required by this part shall be maintained so that data therein can be used for evaluating at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations..."*
- **Important to use product experience to improve your product and process in a timely manner.**



Case 4: Laboratory System

Takeaways:

- Don't assume what worked before will work under different conditions.
- Evaluate data to determine the need for changes in drug product specifications.





Case 5: Materials System

Background:

- Firm makes an injectible drug.
- Multiple adverse events and complaints which indicated presence of endotoxin
- FDA inspected the firm.
- Firm had not identified a root cause.
- Firm started to test for endotoxin in-process, prior to terminal sterilization, “for information only.”
- Firm had found in-process results that were OOS, but finished product tested in specification.



Case 5: Materials System

What Happened:

- **FDA questioned the firm on the high in-process results.**
- **As a response to the investigators, the firm ceased in-process testing for endotoxin.**





Case 5: Materials System

What Happened Next:

- **FDA issued a Warning Letter.**
- **After discussions with FDA, firm recalled the product.**
- **As a corrective action, the firm worked with the agency to develop a work plan to find the source of the endotoxin.**
- **Eventually the firm determined that the endotoxin came from a raw material, and that the toxin was able to make it through the manufacturing process.**



Case 5: Materials System

Takeaways:

- “Quality cannot be tested into products; it should be built-in or should be by design”
- Raw materials (including excipients), container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.





Case 6: Materials System

Background:

- Firm makes a tablet product containing a dissolution aid.
- Supplier announces it will be discontinuing dissolution aid.
- Firm analyzes other sources and finds a “like for like” substitute.
- Firm initiates plant trial to evaluate material change.
- Testing for trial batches will require some time.
- Firm decides to manufacture multiple lots for market with new dissolution aid without having complete data from the trial batches.



Case 6: Materials System

What Happened Next:

- **QC testing showed that all product intended for market made with the new aid failed.**
- **All product with the new aid intended for market had to be destroyed, costing the firm millions of dollars.**
- **Firm bought all of the original dissolution aid on the market and now has a year's worth in stock.**
- **Firm is still working to find a solution.**



Case 6: Materials System

Takeaways:

- **Do not manufacture at risk.**
- **Two materials meeting the same compendial specifications are not necessarily equivalent for use in manufacturing your product.**
- **Limit exposure to supply chain risks by qualifying multiple sources of raw materials.**
- **Knowing and understanding your supply chain can prevent problems.**



Case 6: Materials System

Takeaways:





Case 7: Production System

Background:

- Firm manufactures a chewable tablet.
- Routine stability testing found some tablets had 3 times the target of API.
- Release testing had not detected the problem.



Case 7: Production system

What Happened:

- Firm immediately recalled all product.
- Firm determined that different particle sizes, densities, and flow properties caused the blend to desegregate during blender discharge.
- Firm worked to correct problem by reducing “free fall”.
- Firm also implemented these corrections to other products with the same problem.



Case 7: Production System

Takeaways:

- For pre-compression blending, firm should evaluate uniformity of the material entering the press.
- Investigation should be extended to other batches, other products, and other points in the process.
- Release testing may not be a reliable method for catching process problems.



Case 8: Quality System

- **Contractors are being used frequently in the pharmaceutical industry.**
- **Contractors have responsibilities, but so do the companies that utilize them.**
- **This case is not about the contractor, but the firm who utilized them.**



Case 8: Quality System

Background

- **Firm utilizes multiple contract manufacturers to make the products they market.**
- **Several of their contract manufactures have received Warning Letters for CGMP problems.**
- **Review of material from contractors consists only of checking if a Certificate of Analysis is present.**



Case 8: Quality System

What Happened

- **FDA inspects the firm.**
- **Sees that products from contract manufacturers are not reviewed vs. specifications.**
- **Multiple complaints and stability failures were inadequately investigated.**
- **FDA issues Warning Letter for CGMP deficiencies including lack of oversight by the quality unit.**



Case 8: Quality System



Suddenly, a heated exchange took place between the king and the moat contractor



Case 8: Quality System

Takeaways:

- **Firms who market their products are ultimately responsible for the quality of their products, regardless of who manufactures them.**
- **Manufacturers are responsible for the quality of their products and the reliability of associated test results regardless of who tests them.**



Case 9: Quality System

- **Knowledge Management is not as simple to implement as it sounds**
- **To help give some perspective on this topic, we're going to review 2 examples:**
 - 1. Intra Site – Within one site**
 - 2. Inter Site – Between multiple sites**



Case 9: Quality System

Intra Site: Background



- Firm makes an API
- A Customer identifies low levels of contamination using a new test method.
- Complaint regarding contaminant relayed directly to the firm's R&D department.
- R&D department started an investigation.
- The quality group wasn't notified when the complaint was received.



Case 9: Quality System

Intra Site Example: What Happened



- FDA inspection revealed that the R&D investigation did not address affected products on the market.
- The firm ultimately recalled.
- Warning Letter issued citing failure to thoroughly investigate complaints.



Case 9: Quality System



Inter Site Example: Background

- A pharmaceutical manufacturer has multiple sites.
- One site was inspected in late 2008 and received a Warning Letter in early 2009
- Citations included:
 - Failure to thoroughly investigate batch failures.
 - Failure to submit Field Alert Reports (FARs).
- Another site was inspected mid 2009 which found:
 - Failure to thoroughly investigate batch failures.
 - Failure to submit FARs.



Case 9: Quality System

Inter Site: What Happened



- **FDA placed both sites under import alert within two weeks of the second inspection.**
- **Warning Letter issued for the second site regarding, “several violations that are identical to those found” during the inspection of the other facility.**
- **Firm voluntarily recalled over six hundred batches of various products.**



Case 9: Quality System

Takeaways:

- **Communication is key**
 - not only within a single location, but between multiple locations
- **Knowledge dissemination not only useful within a company, but beyond as well.**



Case 10: Quality System

Background:

- **Three Firms: A, B, and C**
- **These firms manufactured products under NDAs, ANDAs, and Monographs.**
- **Both prescription and OTC products.**



Case 10: Quality System

Firm A:

- **For a coated tablet, operators determined the end point of the coating cycle visually.**
- **In a two year period, over 150 batches failed for dissolution, with a suspected root cause involving under- and over-coating.**
- **Firm utilized release testing to support partial lot releases of over 60 batches.**



Case 10: Quality System

Firm B:

- **Firm manufactures multiple tablet products.**
- **Firm had problems with tablet coating, shape, color, impurities, and uniformity of finished product.**
- **Routine practice involved resorting to remove the nonconforming tablets they could find and releasing “conforming” product.**



Case 10: Quality System

Firm C:

- **Found raw materials with high levels of impurities.**
- **Problems with tablet shape, uniformity, etc. with up to 75% rejection rate.**
- **Complaints were received over a period of years**
- **All of these practices were cleared by upper management.**



Case 10: Quality System

What Happened:

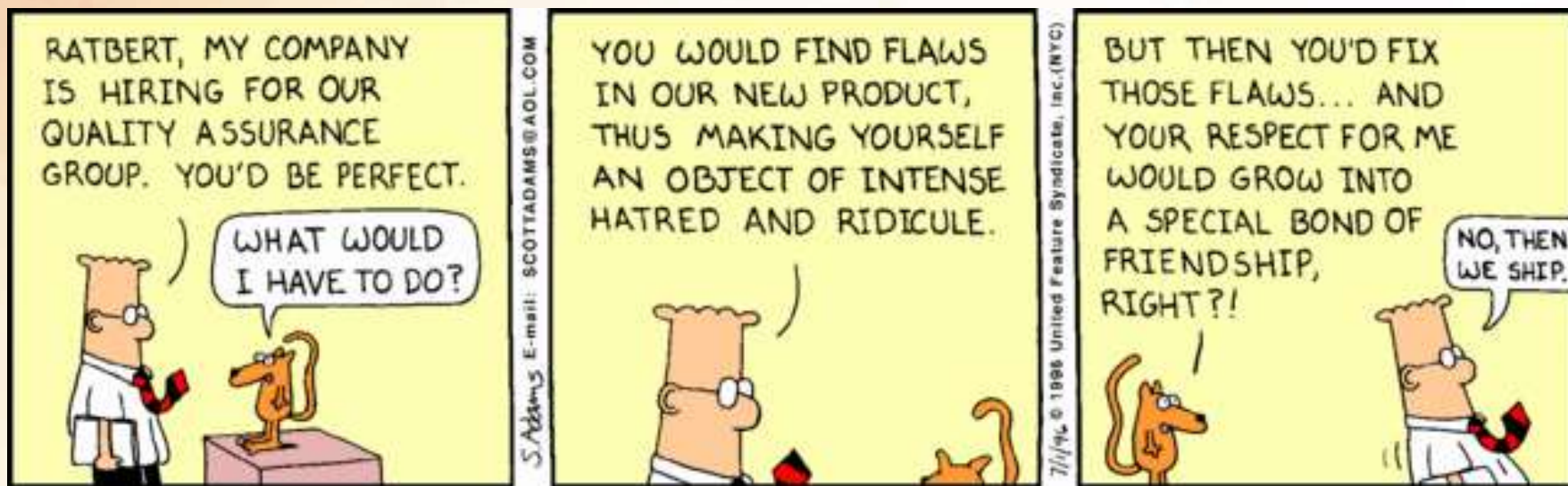
- **Firm A:**
 - Warning Letter, Recalls
 - Multimillion dollar fine
 - Culminated in a Consent Decree
- **Firm B:**
 - Warning Letters, Recalls
 - Criminal Investigations
 - Site shutdown by parent company
- **Firm C:**
 - Warning Letter, Recalls
 - Multimillion dollar fine
 - Seizures
 - Culminated in Permanent Injunction



Case 10: Quality System

Takeaways:

- “Quality cannot be tested into products; it should be built-in or should be by design”





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Questions?

For more CGMP information...

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm>

Evaluation: surveymonkey.com/r/CGMP-D2S4



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