# Production and Process Controls: Case Study

**FDA Small Business Regulatory Education for Industry (REdI)**

Silver Spring, MD
August 28, 2020

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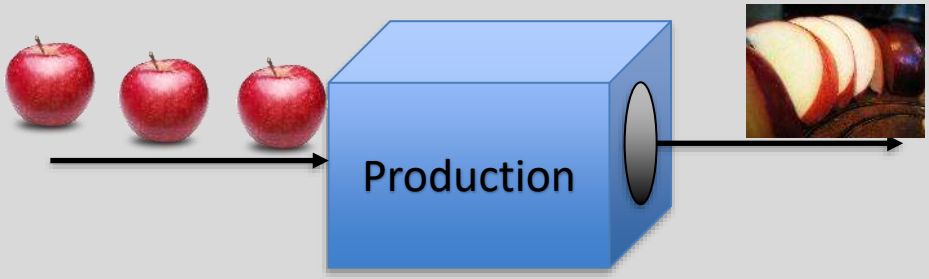
# Production and Process Controls: Why Are They Important?

Manufacture products that meet pre-determined specifications




Production line that produces product that meet pre-determined specifications


Production line that produces product that DOES NOT meet pre-determined specifications

# Learning Objective

Describe how to implement effective production and process controls, using a case study.

# Production and Process Controls: Titles and Regulation Number

| Subpart | Title | Regulation Number (21 CFR) |
|---|---|---|
| **Production and Process Controls** | Production and Process Controls | 820.70 |
| | Inspection, Measuring and Test Equipment | 820.72 |
| | Process Validation | 820.75 |

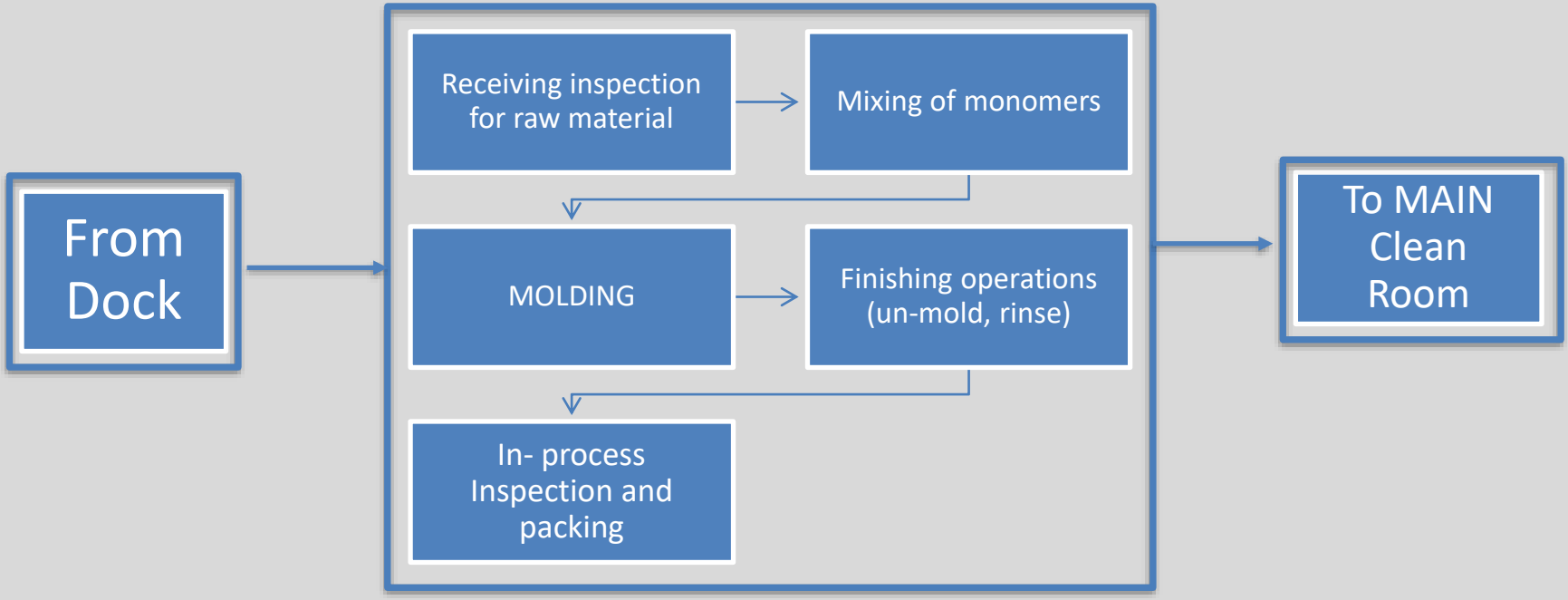
# Hydrogel

Photo by Petra Klawikowski - Own work, CC BY-SA 3.0,
https://commons.wikimedia.org/w/index.php?curid=53561504

Used in:

- Drug delivery
- Specialty coatings
- Contact lens

# Hydrogel Processing



# General Production and Process Controls

If deviations to specifications could occur as a result of manufacturing, include

1. ***Documented instructions, SOPs and methods***

*CASE STUDY:* Instructions for Hydrogel component mixing, mold drawings, molding, cleaning

21 CFR 820.70

# General Production and Process Controls

Example of **NOT** Documenting critical steps:

- During research and development, small batches of solution were mixed
- No criteria for storing the mixing solution was documented
- During transfer, one of the first failures we encountered was unable to mold the hydrogels as mixing solution had polymerized on the shelf.

# General Production and Process Controls

If deviations to specifications could occur as a result of manufacturing, include

***2. Monitoring and control of process parameters***

*CASE STUDY:* Time and temperature are critical parameters for the molding of the hydrogels

21 CFR 820.70

# General Production and Process Controls

If deviations to specifications could occur as a result of manufacturing, include

***3. Compliance to reference standards***

*CASE STUDY:* Hydrogel manufactured in a Class 1000 clean room:

- Adhere to specified clean room requirements
  (ISO 14644 – 1: Clean room classifications)
- ISO 13485: 2016 - Quality management for medical devices

21 CFR 820.70

# General Production and Process Controls

If deviations to specifications could occur as a result of manufacturing, include

***4. Approval of process and equipment***

*CASE STUDY:* Example:

- Special injection molding equipment
- Approve Equipment Qualifications (example: Installation Q/Operational Q)

21 CFR 820.70

# General Production and Process Controls

If deviations to specifications could occur as a result of manufacturing, include

***5. Criteria for workmanship***

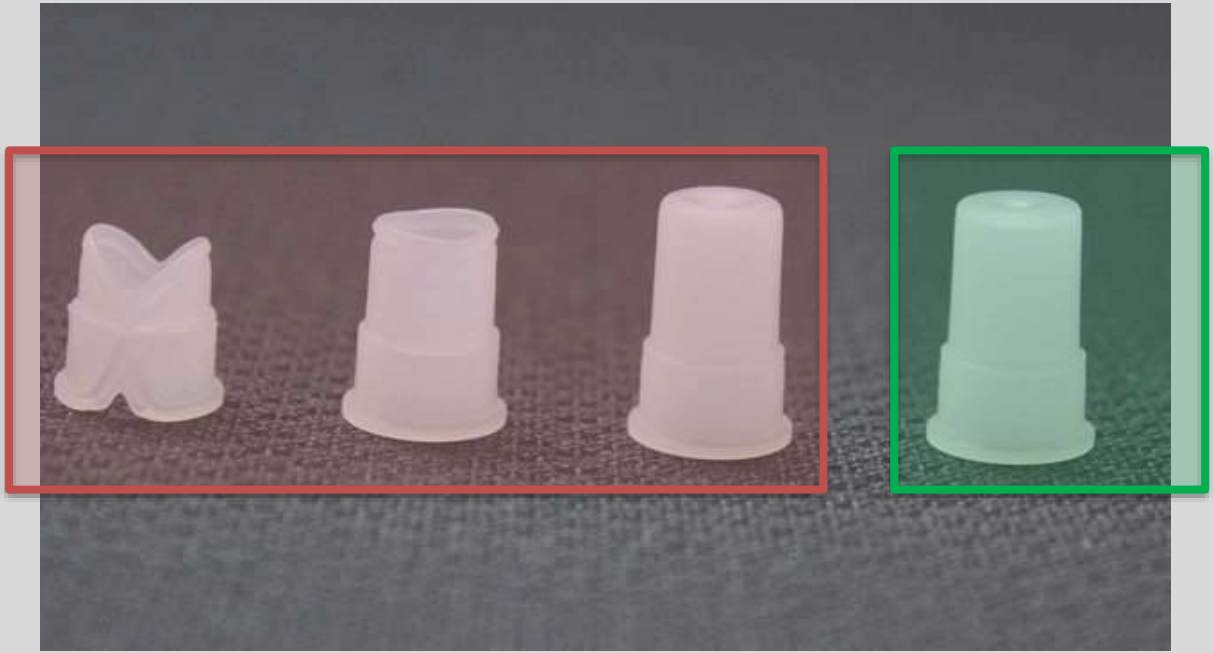
*CASE STUDY:* Example:

- Pictures of acceptable and not acceptable product

21 CFR 820.70

# General Production and Process Controls

Not Acceptable



Acceptable

Photo Credit – Nexpcb

# Product and Process Changes

*CASE STUDY:* Change in supplier of one of the monomers

- Qualify the supplier based on the risk of the component and purchasing control procedures (21 CFR 820.50)
- Verify or validate (where appropriate) changes before implementation (per 21 CFR 820.75)
- Approve changes (per 21 CFR 820.40)

# Environmental Control

- Humidity is key for production of the hydrogel
  - Requires use of special humidity chamber where humidity can be controlled with 5% variance

21 CFR 820.70 (c)

# Environmental Control

- System to record humidity charts during operation
- Review humidity chart to make sure the humidity levels are within operating window


Photo Credit – Thomas Sci

21 CFR 820.70 (c)

# Knowledge Check

**What system can you use to control humidity for making hydrogel?**

a. Thermometer

b. Humidity Chamber

c. Laminar flow hood

# Personnel

- Hydrogel manufactured in a Class 1000 clean room
- Adhere to specified clean room requirements (ISO 14644-1)

21 CFR 820.70 (d)

# Personnel

**Examples of some personnel characteristics:**

- Clothing requirements (for manufacturing hydrogel):
  - Hair nets, smocks, shoe covers, gloves
- Personal hygiene requirements:
  - No make up, beard covers
  - Separate wash station

# Personnel

**Examples:**

- Restrict food and drink areas
- Address illnesses at work
  - Respiratory, skin conditions


Photo credit - CC BY-SA-NC

# Personnel

- When entering the clean room, such as:
  - Janitorial staff
  - Technicians who come to work on machines
- Must be:
  - Trained on the clean room requirements, OR
  - Supervised by a trained individual

21 CFR 820.70 (d)

# Knowledge Check

**What do you need to do when machine technicians need to enter the cleanroom?**

a. Train them

b. Nothing

# Contamination Control

- **Cardboard Boxes**
  - Particulate from cardboard boxes may end up in the hydrogel
  - Do not store cardboard boxes in clean room

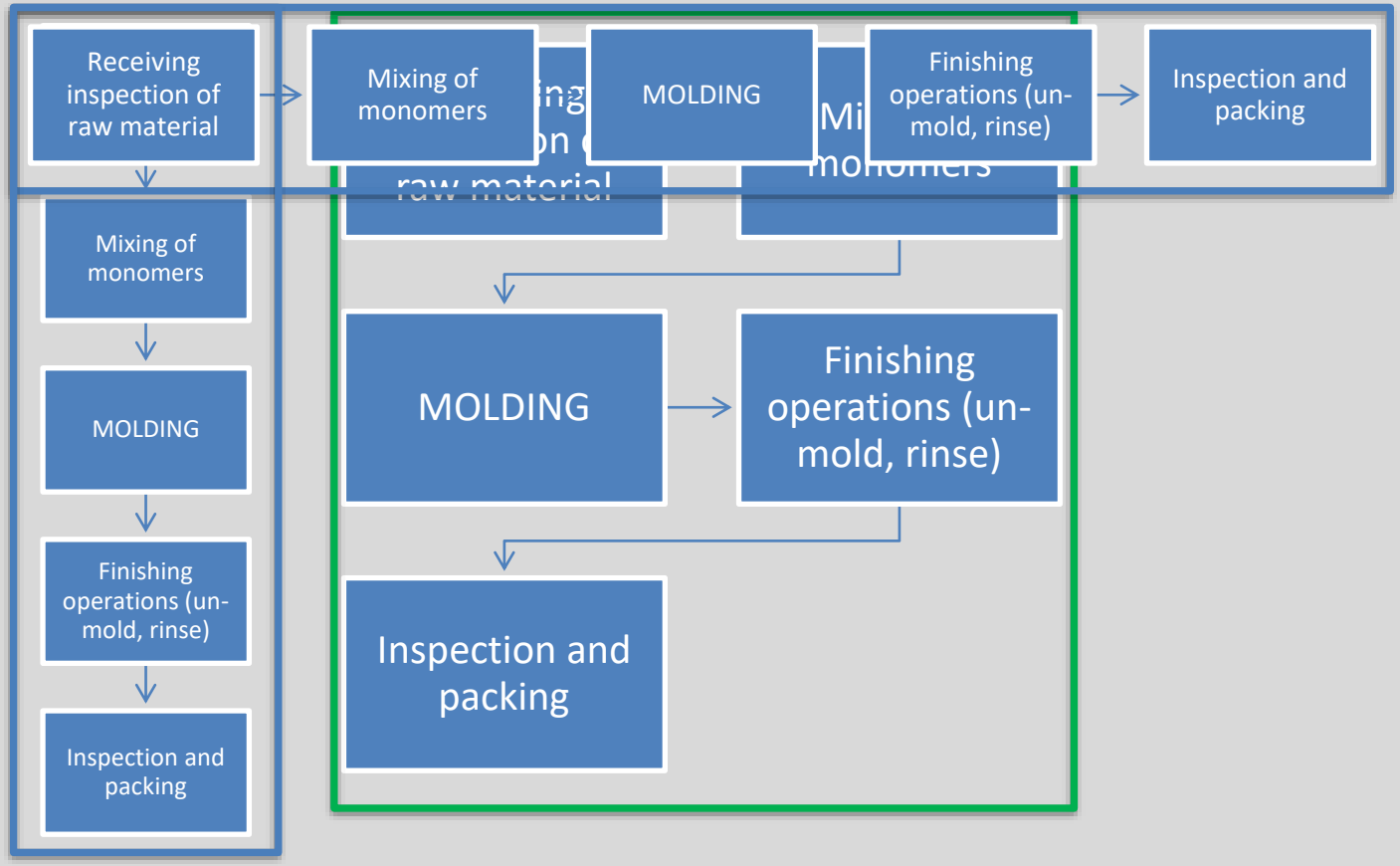
21 CFR 820.70 (e)

# Buildings

- For the hydrogel processing, ensure sufficient space to perform necessary operations: Mixing, molding, cleaning
- Examples:
    - Process Flow diagrams, space analysis

21 CFR 820.70 (f)

# Buildings


Receiving inspection of raw material
Mixing of monomers
MOLDING
Finishing operations (un-mold, rinse)
Inspection and packing
Mixing of monomers
MOLDING
Finishing operations (un-mold, rinse)
Inspection and packing

# Buildings

- Prevent mix ups of different sizes and composition of the hydrogels
  - Different colored bins for different sizes or compositions
  - Line clearance procedures
- Assure orderly handling for the move from the auxiliary molding room to the main clean room
  - Stacking trays
  - JIT (just in time) processing for moving

21 CFR 820.70 (f)

# Equipment

Ensure that all equipment used in manufacturing process is:

- Appropriately designed, constructed, placed, and installed
- To facilitate maintenance, adjustment, cleaning and use
- Meets specified requirements
  - Mixer,
  - Injection molding,
  - Ultrasonic cleaner

Examples:

- IQ/OQ/PQ (installation, operational, and performance qualification)
- Checklists for all functions

21 CFR 820.70 (g)

# Equipment Maintenance Schedule and Inspection

- Establish, maintain schedules to adjust, clean and otherwise maintain equipment and conduct inspection
  - Examples:
    - SOP for equipment maintenance
    - Line clearance procedures
    - Checklist at beginning of shifts
- Document these activities
  - Examples:
    - Equipment Logs or LHR or Traveler

21 CFR 820.70 (g)(1)- (2)

# Equipment Adjustment

- Post any inherent limitations or allowable tolerances
  - visibly or near equipment requiring periodic adjustments

- Make information readily available to persons performing adjustments
  - line clearance procedure
  - QA procedure
  - set up procedure

21 CFR 820.70 (g)(3)

# Manufacturing Material

- Material used in the manufacturing process, or byproduct produced during manufacturing, that was not the design or intent of the manufacturer

- If the manufacturing material has an adverse effect on product, then they need to be removed

21 CFR 820.70 (h)

# Manufacturing Material

- Remove unpolymerized monomers and solvents
  - through repeated rinsing, ultrasonic cleaning

21 CFR 820.70 (h)

# Validate Automated Processes

- Examples of automated process during hydrogel manufacturing
  - Injection molding process
  - Statistical process control software
  - Complaint tracking software
  - Inventory tracking
  - Document control

21 CFR 820.70 (h)

# Summary

Make sure you document and monitor production and process controls when manufacturing hydrogel to avoid device failures

# Resources

| Slide Number | Cited Resource | URL |
|---|---|---|
| 5, 8, 10 -13, 16,17,19, 22 - 24, 26 -31 | Quality System Regulation and Preamble | www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1<br><br>www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm |
| All | Inspection Guide | https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074899.htm |
| All | Guide to Inspections of Quality Systems [Quality System Inspection Technique (QSIT)] | www.fda.gov/iceci/inspections/inspectionguides/ucm074883.htm |

# Questions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