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Avoiding Pitfalls and 483s in Medical Gas Transfilling

Presented by: Randy Hughes, RRT

What is transfilling?

- Transferring a gas, either in a liquid or gaseous state, from a larger container into smaller containers (i.e., high-pressure cylinders or cryogenic vessels)
  - Examples
    - Gas to Gas (Cascading)
    - Liquid to Gas
      - Stand tank to Cylinders
      - Large Cryogenic Vessel (LCV) to cylinders
    - Liquid to Liquid
      - Stand tank or LCV to “smaller’ vessel”
        - Vehicle Mounted Vessel (VMV)
        - Cryogenic Home Vessel (CHV)
- Today’s focus is mostly on cylinder filling

Significance of Transfilling

- Manufacturing of a “drug”
  - Manufacturing must conform with Federal Law – Code of Federal Regulations (CRF Title 21 United States Code)
    - Part of which is commonly known as Food, Drug and Cosmetic act
      - Referred to at the Current Good Manufacturing Practices (cGMP’s).
  - Enforced by Food and Drug Administration (FDA)
  - Noncompliance can result in:
    - Product quarantine
    - Product seizure
    - Operation shut-down
    - Civil and Criminal penalties

What is a 483?

- An FDA form 483 is used by investigators to document findings found during an investigation that may constitute violations of the Food Drug and Cosmetic Act.
- The 483 notifies a company of the findings for which they must devise and implement a corrective action plan.

Common FDA Deficiencies (483s)

- There are many FDA deficiencies (483's) that can be noted during the transfilling process, we will discuss the most common.
  - Adulterated Product
    - Any drug which is not recognized in an official compendium* is adulterated if its strength differs from, or its purity or quality falls below that which it purports or is represented to possess, when tested by scientifically sound methods.
    - Any purported drug that was produced in a manner that calls into question the strength, purity or quality
      - Made from "bad product"
      - Made in a facility or manner that could result in improper strength, purity or quality

*Compendium – "a collection of concise but detailed information about a particular subject, especially in a book or other publication." In this case the publication is the United States Pharmacopeia (USP).

Common FDA Deficiencies (483s)

- Mis-Branded product
  - “Labeling” is false or misleading in any particular manner
  - Place of business (manufacturer, packer or distributor) is not clearly obvious
  - Ordinary person cannot understand name of the drug or the product/content of the vessel

Common FDA Deficiencies (483s)

- Facility
  - Cleanliness
  - Condition of fill system
  - Lighting
  - Storage designation
  - Security

Common FDA Deficiencies (483s)

- Analyzer calibration
  - Calibration Gases
  - Certificates Of Analysis (COA)
  - Following manufacturer guidelines
    - Battery
    - Flow/pressure
    - Stability
  - Evidence of up-to-date Preventive Maintenance (PM)

Common FDA Deficiencies (483s)

- Incoming product documentation
  - Certificate of analysis (COA)
  - Testing?
- Label control process
  - Ordering
  - Count
  - Security
- Staff training
  - cGMP
  - “Ongoing”

Common FDA Deficiencies (483s)

- Filling process
  - Staff knowledge of fill system components
  - PPE
  - USP label
  - Zero verification of vacuum pump
  - Nitrogen (N2) re-pressurization
  - Heat of compression
  - Temperature/Pressure conversion chart

Common FDA Deficiencies (483s)

- Batch Production Records
  - Errors and error correction
  - Filler signature
  - Quality Control Unit (QCU) review of each batch
  - Check marks vs actual number (digit)

Common FDA Deficiencies (483s)

- Post fill
  - Leak test
  - Hold for release
  - QCU review

Minimizing Exposure

- Random unannounced audits of actual fill
  - Robust record review audits
    - Analyzer calibration logs
    - Label control logs
    - Batch production records
    - PM and testing records
    - Include as part of Performance Improvement activities
  - Train, Train again, verify and re-train as necessary

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Questions?