Good Manufacturing Practices

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Good Manufacturing Practices

- PET Manufacturing is very different from conventional manufacturing
- Usual practices are not applicable
- Tests which must be carried out are very different

Batch Size

- PET Drug Products
  - Single Vial
  - Short-lived gases and liquids
  - Usually no more than 10-12 clinical units
- Conventional Drug Products
  - Thousands of packaged units or dosage units

Expiration Date

- PET Drug Products
  - Minutes to hours
  - minimum concerns over decomposition
  - Accelerated stability testing not necessary
- Conventional Drug Products
  - Months to years
  - Must test for decomposition products using accelerated storage conditions

QC Testing

- PET Drug Products
  - Must be performed and completed within minutes to 1 hour
  - Sample usually drawn from single vial batch
  - Tests not completed prior to distribution
- Conventional Drug Products
  - Testing on large representative samples from a large batch
  - Testing complete prior to distribution

Environmental Concerns

- PET Drug Products
  - Manufacturing accomplished in ambient environment
  - Sterilization accomplished by filtration at point of filling
- Conventional Drug Products
  - Open vial filling lanes require a class 100 environment
  - Active microbial and nonviable particle counting necessary

Personnel

- PET Drug Products
  - Generally highly educated scientists and professionals responsible for production
  - Often a single individual present for entire process
- Conventional Drug Products
  - Personnel with less training who require close supervision

Radiation Concerns

- PET Drug Products
  - Radiation safety must take precedence over other issues of GMP when defining manufacturing processes and testing
- Conventional Drug Products
  - None

Theoretical Yields

- PET Drug Products
  - Usually the percentage of radioisotope incorporated into the final product
  - Radiochemical may vary with causes which cannot be determined
- Conventional Drug Products
  - Based on expected theoretical number of dosage units produced from a known weight of ingredients

Sterilizing Filters

- PET Drug Products
  - Usually dilute aqueous liquids up to 30 mL volume
  - No filter compatibility issues have been identified
  - Most PET centers use the same filters
- Conventional Drug Products
  - Filter validation and compatibility issues are important

Control and Reconciliation of Materials and Components

- PET Drug Products
  - Inventory reconciliation not feasible or necessary
  - Accidental excess or shortfall may not affect radiochemical yield
- Conventional Drug Products
  - Inventory reconciliation important to identify potential miss-formulation of batch
  - Help prevent distribution of bad batch

Product Strength

- PET Drug Products
  - Strength is usually expressed as specific concentration at EOS
  - Strength changes continually after production
- Conventional Drug Products
  - Strength expressed in unit of weight or biological activity per volume or unit of weight per dosage unit
  - Strength is fixed

In Process Sampling and Testing

- PET Drug Products
  - No opportunity for sampling in process
  - Possible to monitor some steps in automated computer driven processes
- Conventional Drug Products
  - Opportunity to sample in-process materials at multiple points in the manufacturing process

Holding and Distribution

- PET Drug Products
  - Holding not applicable
  - May be shipped prior to completion of all QC tests
  - Only option is to recall product prior to delivery of product
- Conventional Drug Products
  - Holding and warehousing of finished product requires careful segregation and control of storage conditions
  - May last days to weeks

Drug Product Inspection

- PET Drug Products
  - Visual Inspection limited due to radiation concerns
  - Cannot inspect for fine particulates
  - Can inspect for approximate volume, gross particulates and color.
- Conventional Drug Products
  - Particulate inspection of 100% of units possible
  - Inspection for seal integrity, gross and microscopic particulates possible.

Buildings and Facilities

- Basic requirements are similar
- "…shall be of suitable size, construction and location to facilitate cleaning, maintenance, and satisfy its intended purpose and for proper operations."

Renovations at BNL for GMP

- Build a new room for GMP preparations
- Make the GMP room meet all FDA specifications
- Use the GMP room for preparation of all radiopharmaceuticals for humans

Aseptic Processing and Sterility Assurance

- Laminar flow hoods
  - filter integrity checks
  - flow checks
- Disinfection
  - types of flooring
  - wall materials
  - ceiling restrictions

Aseptic Processing and Sterility Assurance

- Environmental monitoring
  - SOP for culture collection
  - SOP for cleaning procedures
- Validation of techniques
  - time frame for validation
  - SOP for TLC, HPLC etc.

Process Validation and Control

- Process variables
  - which are important (sufficient)
  - development of SOPs for testing
  - what documentation is required during the run
- Changes in process variables
  - what steps need to be taken
  - SOPs for changing process variables
- Historical results
  - how can these be used (FDA CDER 1990)

Quality Control and Drug Product Stability

- Separation of manufacturing and QC
  - final decision to reject a product
  - release before completion of testing
- Yield limits
  - which variables are acceptable
  - how do we handle short runs (% theoretical ?)
- Critical components
  - how are these defined

Quality Control and Drug Product Stability

- Written procedures
  - identity
  - strength
  - quality
  - purity
  - deviations recorded and justified
- Equipment identification
  - phase of processing?
  - identification for batch record

Documentation and Other GMP Topics

- Documentation
  - forms versus SOPs
  - lot number recording
  - packaging and labeling
  - building cleaning documentation
- Exceptions to cGMP
  - second person checks
  - computer recording of process variables
  - using manufacturer's certification or analysis

Building design considerations

- Air flow requirements
  - how small can we make the laminar flow area
  - how small can we make the positive pressure area
  - can the laminar flow areas be positive and the room negative
  - how about humidity and temperature control
  - intake filters
  - outflow filters on hoods
- Walls and Ceilings
  - what are the sterility requirements
  - what is acceptable for a ceiling
  - how can the block walls be upgraded

Building design considerations

- Lighting fixtures
  - which are permitted
- Holding areas for uncertified materials
  - how far away from manufacturing areas
  - what administrative controls are required

Building design considerations

- Plumbing
  - certification of leak free system
  - how often must this be checked
  - is plumbing equipped with device to prevent back siphonage
- Sanitation
  - insect infestations
  - mice
  - SOPs for inspections and use of insecticides

Equipment

- Automatic or Electronic equipment
  - what is routine calibration
  - how extensive do the records need to be
  - what is the level of computer security
  - How is the computer program validated
- Sterilizing Filters
  - SOP for burst pressure test

Equipment

- Containers and Closures
  - which are acceptable
  - how are they validated
  - retesting

Summary

- The cost to come into compliance can be substantial
- Compliance will probably be graded from strictest for commercial suppliers to slightly less stringent for research operations