Challenges in the Regulatory Approval of Parenteral Drugs.

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Outline

The most common deficiencies found in generic submission for parenteral drug products will be discussed for

• Overall documentation
• Active Pharmaceutical Ingredients (API)
• Drug Product
• PM
Overall Documentation

• Common deficiencies in DMF
  – Starting material
  – Purification
  – Sterilisation processes

• Pre-evaluation of DMF should reduce the # of NONs
Documentation (cont’d)

• Documentation to be submitted for the drug product
  – C/As for 2 batches / presentation
  – Batch size: minimum pilot scale
  – Executed batches for the batches used in the pharmaceutical equivalence studies
  – Stability for 2 batches / presentation
API

Additional tests required in the specifications:

• Non-sterile API:
  – Heavy metal test
  – Bacterial endotoxin test

• Sterile API
  – Heavy metal test
  – Bacterial endotoxin test
  – Sterility
API

Common issues with sterile APIs:
• Manufacturing process
• GMP compliance for the manufacturing site
• Container closure system
• Stability
Sterile APIs

• Manufacturing process
  – Sterilization/Depyrogenation parameters for all equipments and container closures
  – Validation reports for non standard cycles
  – Filter validation
  – Lyophilization
Sterile APIs

• GMP status
  – API manufacturing site
  – Third party contractor used to sterilize the container closure system
  – Should have been established with the Health and Food Products Branch Inspectorate prior to filing
Sterile APIs

- **Container closure system (CCS)**
  - should be treated like CCS for sterile finished drug product

- **Stability**
  - Controls used to maintain sterility during storage and transportation
Parenteral Drug Products

Common issues with parenterals:

• GMP compliance
• Development / Validation
• Manufacturing process
• Container closure system
• Stability
GMP status

- Drug product manufacturing site, packaging site and testing site
- Third party contractor used to sterilize the container closure system
- Should have been established with the Health and Food Products Branch Inspectorate prior to filing
Parenteral Drug Products

Common issues with parenterals:

- GMP compliance
- Development
- Manufacturing process
- Container closure system
- Stability
Development

- Pharmaceutical Equivalence\(^1\&\(^2\)
  - Definition under C.08.001.1
- Manufacturing process
- CCS
- Microbiological Attributes
- Compatibility with diluents

1. Submissions for Generic Parenteral Drugs
2. Draft Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions
Pharmaceutical equivalence

Pharmaceutical Equivalent To CRP

• Comparative formulation and chemical equivalence
  – Identical quantities of chemically equivalent medicinal ingredient in an identical parenteral dosage form

• Comparative analytical profiles
  – Including specified and unspecified impurities

• Comparison of physicochemical properties
  – pH, specific gravity or density, osmolality/osmolarity, surface tension and buffering capacity
Development

• Manufacturing process:
  – Rational for choosing a particular drug delivery system
  – Justification for the choice of sterilisation method
  – Developmental work undertaken to protect the drug from deterioration
Development

• CCS:
  – Suitability
  – Container closure integrity
  – Coring studies for multi dose containers

• Microbiological Attributes
  – preservative effectiveness at the proposed concentration and at the end of shelf-life
  – In use period for multi-dose format
Development

• Compatibility
  – With the diluents recommended in the PM
  – For the storage period (24 hrs @RT, 72 hrs refrigerated)
  – In the packaging recommended in the PM
  – For the concentrations recommended in the PM
Parenteral Drug Products

Common issues with parenterals:

- GMP compliance
- Development
- Manufacturing process/Validation
- Container closure system
- Stability
Manufacturing Process

- Critical steps & In-process controls
- Sterilisation/depyrogenation processes
  - Sterilization parameters for the product and all items in contact with the sterile product
  - Validation reports (heat penetration and performance validation):
    - Results for three consecutive runs
    - Loading chart(s)
Manufacturing Process

• Filter validation report
  – Bacterial retention, chemical compatibility, extractables, absorption
  – Flush volume
  – Filter integrity testing
Manufacturing Process

- Lyophilization parameters
- Description of the steps followed for handling of API/CCS supplied sterile
- SOPs referenced in the Master Production Document
- Siliconization of the stoppers
Process validation

- Three consecutive, production-scale batches
- Specific to the drug product
- Protocol should define testing parameters for critical steps, sampling plans, testing methods, and acceptance criteria
Executed Batches/Master Document

- Consistent with parameters established during development and process validation
- Changes documented (scale up)
- Documents for Canadian market
- Complete (final inspection, reconciliation, packaging…)
- In English or French
Product - Specifications

- Description
- Potency (95-105%)
- Purity
- Preservative content
- Volume/UDU
- Bacterial endotoxin
- Sterility
- pH
Product - Specifications

where applicable

• Particulate matter (all solutions)
• Dissolution (implant, suspension)
• Particle size distribution (suspension-emulsion)
• Osmolarity
• Preservative content
• Resuspendability
Parenteral Drug Products

Common issues with parenterals:

• GMP compliance
• Development
• Manufacturing process
• Container closure system
• Stability
Product - CCS

- Incomplete specifications
  - No ID test, no test for glass treatment
- No drawings or do not correspond
- Missing specifications or drawings
- Incomplete data submitted and no DMF referenced
Product - Stability

• 6M minimum at the time of filing
• Transportation studies or data supporting the transportation conditions and demonstrating that sterility is maintained should be submitted
• Storage recommendation not supported by stability data (e.g., 2-30 °C)
Product Monograph

• Name
• list of diluents and storage containers
• All non-medicinal ingredients
• Standard statements are missing
  – E.g., ‘As with all parenteral drug products, injections/intravenous ad-mixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.’
Questions?
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