2-2 Sterile Product Assessment

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PREQUALIFICATION OF MEDICINES PROGRAMME
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PQP
QUALITY MEDICINES FOR EVERYONE

Focus

- ☺ Overview of Regulatory Requirements
- ☺ Tips for Critical Thinking
- ☺ Issues and Solutions

Regulatory Requirements - Overview

API	FPP	Labelling
Manufacture	Product Development	SmPC
Specifications/Analytical Methods	Unit/Batch Formulation	PIL
Packaging	Manufacturing Techniques	Container Labels
Stability	Process Validation	
Transportation	Specifications/Analytical Methods	
	Packaging	
	Stability	

Labelling

- ☺ Declaration of Sterility
- ☺ Strengths and Presentations
- ☺ Dosage and Administration
  - Routes of Administration
  - Dose/Kg/hr
  - Diluents, Dilution Range and Storage Recommendations
- √ Neat Product
- √ Reconstituted Product
- √ Diluted Admixtures

API

Activity	Requirement
Manufacture	Sterilization Techniques Validation of Sterilization Processes
Specifications	(Sterility) BET
Packaging	Compatibility Container Closure Integrity Sterilization Techniques Validation of Sterilization Processes
Stability	Container Orientation
Transportation	Validation

Issues - Case Study 1

Sterile Cefuroxime Sodium is manufactured at an API fabrication site in country A and shipped to the FPP fabrication site in country B. The API is packaged in plastic bags that are sterilized by gamma radiation at a third party sterilization facility. On receipt at the FPP fabrication site, the sterile API is stored and sampled for testing, in the receiving warehouse where APIs for all dosage forms are quarantined prior to testing and release for use in the fabrication of FPPs. Following an in-depth assessment, you have concluded that the sterilization processes for the API are well documented and validated.

Product Development

Context	Requirement	Critical Elements
Regulations	Pharmaceutical Equivalence	Comparative Physicochemical properties: -Buffering Capacity -Surface Tension -Specific Gravity -Osmolarity
Conditions of Use	In-use Period	Appearance pH Assay Degradation Products Sub-Visible Particulate Matter
	Compatibility with Diluents -Diluents -Dilution Range -Storage Recommendations	

Product Development

Context	Requirement	Critical Elements
Manufacture	Aseptic Processing vs Terminal Sterilization (Conventional and Reduced Cycles)	Appearance pH Assay Degradation Products
Packaging	Container Closure Integrity	Ingress Tests - Dye - Microbial
	Suitability	Extractables/Leachables
Testing	Antimicrobial Preservative Effectiveness	Pharmacopeial Test

Formulation & Manufacturing Techniques

Aspect	Requirement	Critical Elements
Batch Formula	Batch Sizes - Volumes - No. of Units	Declaration of Overages Potency Adjustments Standards for Excipients Excipients not in final FPP Inert Gas, Silicone oil/Emulsion
Manufacture & Controls	Narrative Description Blank BMR Executed BMR	Preparation of Bulk pH Adjustment Hold Periods Fill Volume/Weight Filter Integrity Checks Silicone Treatment Treatment/Sterilization of Equipment, Accessories, Inert Gas, Packaging Materials and FPP Leak Testing, Lyophilization

Process Validation

Activity	Requirement		Critical Elements
Validation (product)	Hold Time	Pre-filtration	Physical and Chemical Characteristics
		Post-filtration	Sterility
	Process	Aseptic	
		Terminal	Temp, Time, F0
	Report on 3 Batches or Protocol & Commitment		Production Scale

Process Validation

Activity	Requirement		Critical Elements
Validation (process)	Filter Validation	Compatibility	Adsorption Extractables/Leachables
		Pore Size	Bacterial Retention
	Equipment & Accessories	CIP & SIP	Temp, Dwell Time
	Packaging Materials	Containers Closures Seals	Temp, Dwell Time, FH, Heat Distribution Studies - Thermocouples - Biological Indicators RAD ETO Residues

Issues - Case Study 2

The comparator product is a lyophilized powder while the proposed generic product is a ready to use solution. The aqueous bulk solution is filtered through a 0.45µ filter, filled in ampoules and terminally steam sterilized validated to deliver a minimum F_0 of 12. Applicant has indicated that pharmaceutical equivalence data is irrelevant since the comparator product is a powder.

FPP Specifications

Aspect	Requirement	Critical Elements
Specifications	Release	ID, Assay Related Substances **Sterility, BET** **Sub-visible Particulate Matter** Preservative and/or Antioxidants **Uniformity of Dosage Units** **Reconstitution Time**
	Shelf-life	Assay, Related Substances **Sub-visible Particulate Matter** **Reconstitution Time** **Weight Loss** **Sterility (C/C Integrity)**

Analytical Methods

Aspect	Requirement	Critical Elements
Analytical Methods	Description Validation	Conventional Elements of Analytical Method Validation
Sterility	Description - Membrane - Thioglycollate Validation	Pharmacopeial
BET	Description - Gel Clot - Turbidimetric - Chromogenic Validation	Endotoxin Limit MVD Lysate Sensitivity Inhibition/Enhancement Results for 3 batches
Sub-Visible Particulate Matter	Description - Microscopic - Light Obscuration Validation	Pharmacopeial

Packaging

Aspect	Requirement	Critical Elements
Packaging materials Types and Sizes: * SVPs, LVPs # Glass, Plastics, Rubber, Al - Ampoules - Vials (stoppers, seals) - Syringes - Pharmacy Bulk Vials - Single Use - Multiple Use	Composition & Safety - MBT - Nitrosamines	Chemical Testing Biological Testing Extractable/Leachable Profiles Coring Studies ID in Specs

Stability

Aspect	Requirement	Critical Elements
Stability	Storage Conditions **Container Orientation** Trade Packs No. of batches Protocol & Commitment	Assay, Related Substances **Sub-visible Particulate Matter** **Reconstitution Time** **Weight Loss** **Sterility**

Exercise

Applicant proposes to market an aqueous solution product in ampoules (glass) and single dose vials (glass with rubber stoppers). Check the relevance of the data elements for each presentation

Data Element	Ampoule	Vial
Reconstitution Time in Release Specifications		
Container Orientation in Stability Studies		
Sterility in Release Specifications	√	√
Nitrosamines in Composition of Packaging		
Container Closure Integrity in Stability Studies		
Biological Testing for Suitability		
Leachables in Stability Studies		

Questions?