Specification for a biological product

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 101007939. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies.

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Specification

Test	Limits	Method
Identity	Comply	QC-1001
Visual inspection	Clear solution	
Content	≥98%	QC-2001
Impurities Total Individual Unknown	 ≤2% ≤1% ≤0.1%	QC-2001
Potency		QC-2001
Microbiological	Sterile	

- A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria
- ICH guidelines Q6B
- A quality control protocol to be applied to all:
  - Produced batches of
    - Active substances
    - Final product
  - Starting materials, excipients, packing materials
- Performed with Pharmacopeia or validated analytical methods

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What do we test

- Identification
  - Appearance
  - Identity of active substance
- Things that could effect efficacy
  - Content
  - Potency
- Things that can affect safety
  - Impurities
  - Endotoxins
  - Foreign particles
  - Sterility
- Product specific tests

Identification

Appearance and description

A qualitative statement describing the physical state (e.g., solid, liquid) and colour of a drug product should be provided.

Identity

The identity test(s) should be highly specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological and/or immunochemical) may be necessary to establish identity.

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Potency

A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include:

- Animal-based biological assays,
- Cell culture-based biological assays,
- Biochemical assays,
- Other procedures such as ligand and receptor binding assays

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Purity and impurities

Potential sources for impurities

- Production
  - Host cell proteins
  - DNA from the host cells
  - Cell culture-derived impurities, inducers antibiotics, serum, and media components.
  - Downstream-derived impurities
  - Particles
- Product related impurities
  - Chemical degradation products
  - Aggregation

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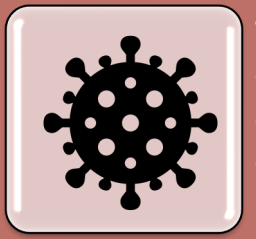
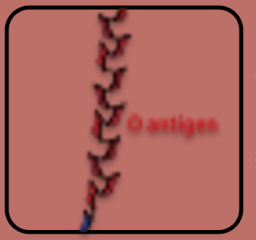
Injectables

- Sterility
- Endotoxins
- Particles



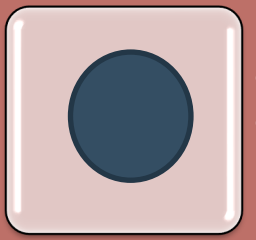
Sterility

- 100% sterility: difficult to measure
- Defined as 1/1millinion
- If a product fail sterility testing if there is not an obvious reason to suspect analytical errors.



Endotoxins (pyrogen)

- Pyrogen: substance gives rise to an elevated body temperature
- Endotoxine Lipopolysaccharides from Gram-negative bacteria. The Limulus Amoebocyte Lysate test (LAL)



Particles

- Tests for visual and sub-visual particles
- See for example United States Pharmacopeia (USP): <788> Particulate Matter in Injections

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In summery

Test	
Appearance	Describing the physical state (e.g., solid, liquid), colour, and clarity
Identity	should be based on unique aspects of its molecular structure and for other specific properties
Potency	A relevant, validated potency assay
Quantity	The quantity usually based on protein content (mass). In cases where product manufacture is based upon potency, there may be no need determination of quantity.
Impurities	If impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined, and acceptance criteria established. **Special issue host cell proteins, DNA, host cell vectors.**
Uniformity of dosage units	
Physical properties	pH, viscosity, osmolality
Safty issues for paranterals	Endotoxins, particles, microbiology, preservatives
Other key components	Antioxidants, metal ions , water content (for non aquas formulations), extractables

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Real World Handling of Protein Drugs – Exploration, Evaluation & Education

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