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PMDA Perspective on Visible Particles in Biopharmaceuticals

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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

- Introduction
  - Japanese Pharmacopoeia (JP, 18th Edition)
  - Approved Matters (Established Conditions) for Foreign Insoluble Matter Test
- Case studies
- Summary

JP in Japanese; https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066530.html
JP in English; https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066597.html

General tests in JP relevant to Visible/Sub-visible Particles

6.06 Foreign Insoluble Matter Test for Injections

6.07 Insoluble Particulate Matter Test for Injections

6.08 Insoluble Particulate Matter Test for Ophthalmic Solutions

6.11 Foreign Insoluble Matter Test for Ophthalmic Liquids and Solutions

6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections

General Rules for Preparations in JP

3. Preparations for Injection

3.1 Injections

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(13) Unless otherwise specified, Injections and vehicles attached to preparations meet the requirements of Foreign Insoluble Matter Test for Injections <6.06>

Foreign Insoluble Matter Test for Injections <JP 6.06>

Foreign Insoluble Matter Test for Injections is a test method to examine foreign insoluble matters in injections.

1. **Method 1.** This method is applied to either **injections in solution, suspension or emulsion, and vehicles for solid injections to be dissolved or suspended before use**. Clean the exterior of containers, and inspect against both a white and a black background for 5 seconds each time with the unaided eyes at a position of light intensity of 2000 to 3750 lx under a white light source: **Injections or vehicles must be free from readily detectable foreign insoluble matters**. As to Injections in plastic containers for aqueous injections, the inspection should be performed with the unaided eyes at a position of light intensity of approximately 8000 to 10,000 lx, with a white light source at appropriate distances above and below the container. The inspection time should be extended accordingly if the inspection is not easy.

2. **Method 2.** This method is applied to **solid injections to be dissolved or suspended before use.** Clean the exterior of containers, and dissolve or suspend the contents with vehicles attached to the preparations or with Water for Injection carefully, avoiding any contamination with extraneous foreign substances. **The solution thus constituted must be free from foreign insoluble matters that is clearly detectable** when inspected against both a white and a black background for 5 seconds each time with the unaided eyes at a position of light intensity of 2000 to 3750 lx under a white light source. The inspection time should be extended accordingly if the inspection is not easy.

Foreign Insoluble Matters

Type	Origin	Example
exogenous or extrinsic	those that are foreign to the manufacturing process	hair, non-process-related fibers, starch, minerals, insect parts, and similar inorganic or organic materials
intrinsic	from within the process	materials from processing equipment or primary packaging, e.g., stainless steel, seals, gaskets, packaging glass and elastomers, fluid transport tubing, and silicone lubricant
inherent	which are known to be or intended to be associated with specific product formulations	particle assemblies (e.g., aggregates)

Modified from USP<1790>

Approved Matters (Established Conditions) for Foreign Insoluble Matter Test in Drug Product Specification

【Specification】

【Test】 : Foreign Insoluble Matter

【Analytical Procedure】

Drug Product meets the requirement of Foreign Insoluble Matter Test for Injections (Method 1) <6.06>

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【Specification】

【Test】 : Remarks

【Analytical Procedure】

Unless otherwise specified, drug product is to be tested according to General Notices, General Rules for Preparations, and General Tests of JP

Case Studies

	Case 1	Case 2	Case 3
Approval Year	2018	2022	2022
Drug substance	Humanized IgG1 produced from CHO cells	Humanized IgG1 produced from CHO cells	Humanized IgG1 produced from CHO cells
Drug Product	Liquid preparation	Lyophilized preparation +vehicle	Liquid preparation
Indication	CD-20-positive Follicular lymphoma	Pruritus associated with atopic dermatitis	Improvement of acute symptoms in pustular psoriasis
Administration route	Intravenous drip infusion	Subcutaneous	Intravenous drip infusion

https://www.pmda.go.jp/PmdaSearch/iyakuSearch/

Case 1 (1)

- Insoluble visible particles (IVPs) were observed in DP long-term stability study as well as the retention samples of all lots produced since 2013
- Root cause and identification of IVPs
  - not observed at the time of release and formed during storage
  - Protein-PDMS* complex (*: derived from rubber stopper)
- Measures taken during development
  - Change of CCS (Container Closure System) and cleaning of rubber stopper
- Appropriateness of the proposed control and shelf-life of DP
  - Safety of identified materials
  - Risk to patients when administered (diluted)
  - Release and Stability specifications

Case 1 (2)

- PMDA’ view
  - IVPs; potential risk factor for immunogenicity
  - Lid evidence from clinical trials due to variability of IVPs among lots

  - Compulsory use of inline filters and its warning in the product information
  - Require to continue to investigate measures to prevent the occurrence of IVPs

Case 2 (1)

- Insoluble visible particles (IVPs) were observed in DP long-term stability study
- Identification of IVPs
  - Cellulose fibers, silicon oil-related particles, protein-silicon complex and protein itself etc.
- Mitigation strategy
  - Some measures have been taken for cellulose fibers
  - Not avoidable to prevent the occurrence of silicon oil-related particles, and the occurrence cause of protein-silicon complex has not been clearly elucidated
  - Frequency of the occurrence may be changed by the condition of medicinal preparation, but difficult to fully prevent the occurrence
- Appropriateness of the proposed control of DP
  - Safety data in clinical trials
  - Foreign Insoluble Matter Test for Injections (Method 2) <6.06> for release/stability specifications
  - For stability specifications, if IVPs are observed, an additional testing is to be performed

Case 2 (2)

- PMDA’ view
  - Difficulty of the interpretation of clinical trial results as the presence of IVPs were unknown in the lots used in the clinical trials, and of identification of adverse events associated with IVPs
  - Appropriate condition of medicinal preparation should be clearly provided in the product information and other relevant document
  - Require to continue to investigate measures to prevent the occurrence of IVPs
  - Require to implement stability monitoring of all lots for the time being to evaluate the frequency of occurrence of IVPs

Case 3

- Product-related particles (PrPs) were observed in DP long-term stability study
- Identification of PrPs
  - Composed of protein and fatty acid
- Appropriateness of the proposed control of DP
  - Presence of PrPs is allowed by the proposed acceptance criteria
  - Visual inspection result is equivalent to characterization studies
  - Particles identified by visual inspection will be routinely verified
  - Use of inline filter at point of administration
- PMDA’s view
  - Acceptable

Summary

- Foreign Insoluble Matter Test for Injections <6.06> is the principal standard (but a minimum requirement) in Japan for the control of visible particles in injections.

- Potential risk factors for the occurrence of visible particles (e.g., formulation, CCS) should be considered at early stage of development.

- If visible particles are detected, identification/characterization, route cause analysis and mitigation strategy should be thoroughly performed.

- In cases where the occurrence of visible particles is not avoidable, control strategy (e.g., release/stability specifications of DP) should be established to achieve “state of control”, based on the above investigation.

- Control of visible particles should be considered throughout product lifecycle

Thank you for your attention!

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