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Risk management of particulate contamination for devices with intravascular access

Gestion des risques de contamination particulaire pour les dispositifs d'accès intravasculaire

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Foreword

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This document was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Medical devices, that are part of the fluid path for delivery directly into circulating blood or are connected to those devices (such as administration or extension sets), include a risk of delivering particulate matter to the patient's body.

These particulates can be created or transferred to the devices during the production or application of those devices and can cause a variety of severe and fatal harms to patients (such as phlebitis, pulmonary emboli, pulmonary granulomas, immune system dysfunction, pulmonary dysfunction, infarction and death).

All parenteral products contain such particulate matter, as it is technically impossible to produce and use these devices without creating or transferring these particles to the devices. This is considered in technical standards and international pharmacopoeias that identify limits of particulate contamination, but these limits can only be considered as a definition of the maximum particle load that is based on current technical state of the art for various particle size ranges.

Several studies and publications imply, that no rationale for any tolerable number for the particulate contamination exists. The occurrence rates of related severe and fatal complications in patients that receive parenteral infusions is closely related to factors such as:

— route of administration;

— particle size and shape;

— number of particles injected;

— particle composition;

— patient population;

— exposure by multiple devices.

Additionally, the current specifications in standards and international pharmacopoeias are omitting the fact, that medical devices and drug containers are typically used in combinations with each other (e.g. container, infusion set, IV-catheter) and/or in parallel (e.g. several infusions running in parallel or in sequence) and/or repeatedly (e.g. several containers/infusion sets being used consecutively). With any of these, the total particulate load that patients receive is an addition of all those sources.

As the complexity of the number of influencing factors and their interrelations do not allow the derivation of any safe level of particulate contamination, the current specifications in standards and pharmacopeia can lead to an inappropriate assumption of safety by manufacturers, regulators, authorities, and clinical practitioners when these levels are met.

This document is intended to provide alternative perspectives on how to control risks related to particulate contaminations and to guide manufacturers, regulators, and authorities into a more comprehensive assessment of the measures related to reducing particulate contaminations.

The leading concept behind this alternative perspective is to apply the general methodology of risk management to identify, assess and control the risks that are related to particulate matter rather than defining an unsubstantiated level of assumed safety.

Risk management of particulate contamination for devices with intravascular access

1 Scope

This document

— provides information on the determination of particulate loads;

— reports on established methods for a comprehensive risk analysis on potential particle sources and related risks in design, manufacturing, and application of devices.

This document is applicable to medical devices that are used to provide intravenous access to patients to deliver liquids.

NOTE For routes of administration that are not intravenous, the information in this document might be relevant to assist in the identification of sources of potential particulate contamination.

2 References

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 14971 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
particle
minute piece of matter with defined physical boundaries

[SOURCE: ISO 14644-1:2015, 3.2.1]

4 Risk management on particulate contamination

4.1 Application of risk management

Medical devices are designed and manufactured in such a way to eliminate or reduce the probability of particulate contamination of the fluid path of the devices and other surfaces which are relevant for the application of the devices.

To identify, assess and control the related risks, the general methodology of ISO 14971 is applied. Annex A lists known sources of particulate contamination of medical devices.

It is expected that medical device manufacturers create or update risk management files to include all relevant and applicable risks from Annex A and implement feasible control measures.

4.2 Determination of particulate contamination

The particulate contamination of infusion sets, and their components and accessories are determined by quantitative testing to assess initial particle loads.

To be able to verify the effectiveness of risk control methods, before or after potential changes, quantitative or qualitative methods are commonly used.

Some of the applicable related methods are described in:

— ISO 8536-4:2019, A.2;

— European Pharmacopoeia 2.9.19, 2.9.20;

— US Pharmacopoeia 787, 788, 790, 1790;

— Japanese Pharmacopoeia 6.07, 6.06;

— ISO/TR 19727.

Annex A
(informative)

Examples for hazards and risk control options related to particulate matter

Table A.1 shows example for hazards and risk control options related to particle matter.

Table A.1 — Example for hazards and risk control options related to particle matter

Risk source group	Source or nature of contamination	Approaches for safe device design	Approaches for safe manufacture	Protective measures in the medical device itself or in the manufacturing process	Protective measures in the manufacturing process	Information for safety
Moulding	Metal parts from tools Mould release agents Flash sprues/gates falling parts Damaged parts (e.g. not fully ejected parts)	Design of moving parts, split line and gates Selection of materials and additives Parts demoulding (avoid drop parts)	Controlled environment (Clean room etc.) Unidirectional air flow over moving parts of mould Peripheral material supply Validated moulding processes Maintenance and cleaning of moulding press/ machines Conveyer systems	Properly specified requirements/limits for geometrical defects (flash, etc.)	Mould preventative maintenance Tool design (i.e. sprue less or runner less designs/hot runners) “Cleaning”, shaking, blowing, vacuum, managing electro-static charge Visual checks/camera control for ejection	Cleaning instructions for equipment
Extrusion	Water bath particulates Chill roll for film extrusion Cutting of tube segments Extrusion head	Filtration system for the cooling water Material selection	Cleaning and maintenance of equipment, tools, extrusion head Sharp, regularly maintained blades for cutting Controlled environment (clean room etc.) – separate areas for the extrusion machine and the post extrusion processing (cooling, coiling) See applicable elements from “moulding”			Cleaning instructions for equipment
Purchasing/ incoming goods	Insufficient control over suppliers and goods “Contaminated” raw materials Sampling (opening/ closing bags) Shipping/transportation from vendor to manufacturer	Double bagging of components	Incoming inspection on particulate contamination (for monitoring and comparison between parts and suppliers) Supplier audits Quality agreements Technical specifications for storage condition Properly specified requirements/limits Procedures for material handling (where, by whom, opening/ closing of bags, in which state is material transported after incoming goods inspections) Documented cleaning and line clearance procedures at the transport company for raw material that is delivered in bulk Separate sample bags being send by a supplier Supplier controls cover the items mentioned before			

Table A.1 *(continued)*

Risk source group	Source or nature of contamination	Approaches for safe device design	Approaches for safe manufacture	Protective measures in the medical device itself or in the manufacturing process	Protective measures in the manufacturing process	Information for safety
Environment	Inappropriate gowning, dressing Airborne particles/ dust	Clean room procedures (monitoring, gowning procedures etc.) Housing of machines Sticky mats at clean room entrance Clean room environmental controls Choice of materials and equipment Layout/design of the facilities		Wipe down procedures at shift change Filtration and monitoring (pressure differential, particle loads etc.) Appropriate gowning rooms and appropriate personnel flow		Gowning instructions Instructions for PPE Instructions for personal hygiene precautions (e.g. Wash and disinfect hands)
Internal transportation	Parts moving in boxes Open boxes Number of manipulations Distance travelled	Closures of boxes Minimize transportation distances and number of manipulations Optimization of package number in boxes	Design and material of transportation devices (plastic vs. carton boxes) Reduce transportation ways and manipulations Control of work-in-progress items (storage, quantities, lean production)	Separate material and personnel flows		
Assembly processes	Snap-fit connections Solvent bonding welding (burnt particles, ultrasonic welding generated particles, welding bulges, etc.) Tube cutting Abrasion of conveyors/ rails material	Design interfaces in such way, that assembly takes place on surfaces that do not allow created particles do enter the fluid path. Weld joint design (Cutting etc.) equipment maintenance	Design and material of transportation devices (belts, trays etc.) Filtered air being used for air showering Cleaning and maintenance of related equipment or machines in appropriate intervals	Inspection of working places to detect potential particle creating during assembly steps Vacuum at tube cutting stations vision systems		
Sterilization	Material being critically affected by the sterilization process	Material properties allowing sterilization with the intended method		Inspection and verification of material properties after sterilization with respect to material integrity, durably and brittleness		
Packaging, labelling, printing	Paper cutting creating particles Particles on the packaging		Packaging in controlled environments Cutting tool maintenance	Material specifications and supplier controls for packaging materials (see incoming goods section) Procedures for unpacking packaging materials and storage for left-over packaging materials		

Table A.1 *(continued)*

Risk source group	Source or nature of contamination	Approaches for safe device design	Approaches for safe manufacture	Protective measures in the medical device itself or in the manufacturing process	Protective measures in the manufacturing process	Information for safety
Storage	Storage conditions not met (direct sunlight) -> degradation of the materials (as far as this degradation could lead to the formation of particles)			Storage conditions specified and validated (humidity, temperature, pressure where applicable)	Storage conditions stated on boxes	
Transportation	Moving parts Travelled distance Vibration Shock Humidity Temperature Pressure Packaging being damaged from the inside by the product → particles can enter	Fixation of movable parts Prevent product design that is likely to damage the sterile barrier system Number of single pouches in a box to avoid too much movement and too much friction/contact between single products Matching box sizes to quantity and size of single pouches etc.		Transportation Simulation/validation Performance requirements for sterile barrier system		
Application/ use	Certain drugs/blood components exclude the use of filters Drug compatibility with device material (precipitation of solution, stress-cracking of device, etc.) Coring of reservoir septum Glass ampules can create particles when opened Incompatible drugs creating clotting/particles Pump tube spallation	Intended use of device vs. presence of inline filters Use filters where not indicated otherwise (consider relevant filtering properties according to the particle sizes being expected) Spike design IV container septum material (also consider inlet-ports)		Check integrity of the device before use Compatibility studies with most representative and "extreme" intended drugs solutions Inspection for pump tube spallation according to		Clearly state contra indications for sets w/o filter Advice for residual risks on labels Recommendation to use IV sets according ISO 8536-4 to be referenced in the Bibliography, i.e. with filters (or use an add-on filter) if not contraindicated by the specific drug