Regulatory Perspectives on Application of ISO 18562 Standards

IPAC-RS Supplier and Pharma
Device and Container Closure System Quality

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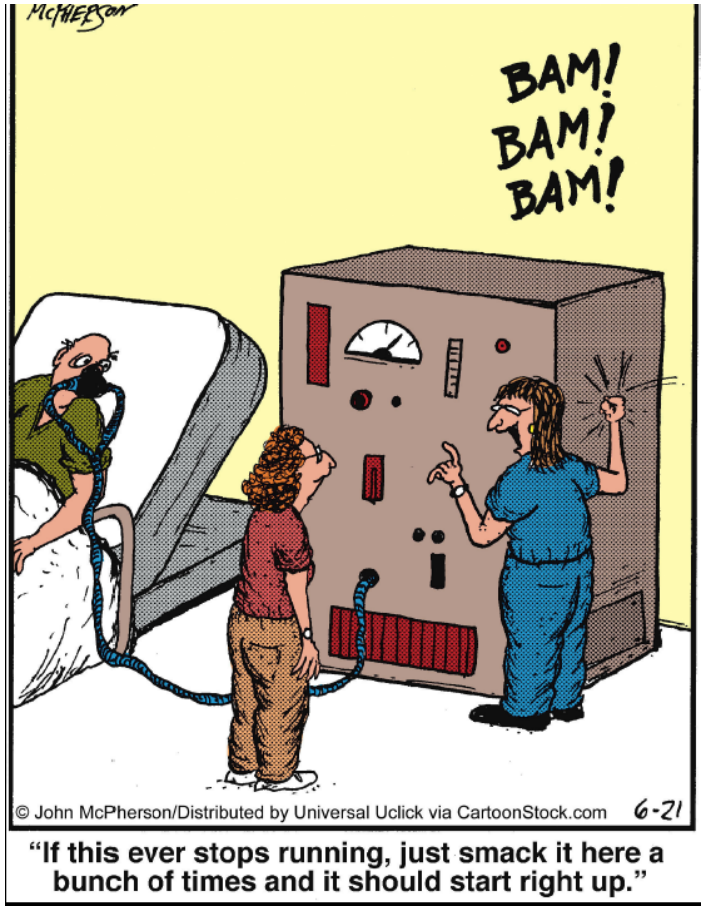
The information provided in this presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Description of respiratory products reviewed by CDRH
- Definition of the respiratory gas pathway
- Highlights of 18562 standards
- Example of a leachable table with practical considerations
- General considerations on best practices

Medical Devices of the Respiratory Gas Pathway



"If this ever stops running, just smack it here a bunch of times and it should start right up."

https://www.fda.gov/medicaldevices/productsandmedicalprocedures/generalhospitaldevicesandsupplies/tubingandluermisconnections/ucm313275.htm

Examples of Inhalation Products that May Be Reviewed by CDRH

- Nebulizers
- Inhalers
- Anesthesia workstations/gas mixers
- Ventilators
- Breathing tubes/filters
- Masks

*For a **drug delivery device and drug** that are developed for marketing to be **used together as a system**, a lead center will be designated to be the contact point with the manufacturer(s). If a drug has been developed and marketed and **the development and studying of device technology predominates**, the principle mode of action will be deemed to be that of the device, and CDRH would have the lead.*

https://www.fda.gov/combinationproducts/jurisdictionalinformation/jurisdictionalupdates/ucm103179.htm

External Communication vs. Respiratory Gas Pathway

External Communication (EC): 10993

Medical device categorization by			Biological effect													
Nature of Body Contact		Contact Duration														
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue*/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Guidance: Published June, 2016

Gas Pathway: 18562

- Definition: Interior surfaces of a device over which gases or liquids can be inspired
- Like EC, classification is indirect contact
- Unlike EC assessments, 18562 provides methods for assessing particulates and Volatile Organic Hydrocarbons (VOCs)
- Unlike 10993, 18562 provides methods for leachables assessment in *condensate*

ISO 18562 Series: Published 2017

ISO 18652 Standards: A Closer Look

- **ISO 18562-1**: Evaluation and testing using a risk management process
  - Scope: Considerations for risk assessment of potential contamination of the gas stream of respiratory gas pathway devices.
  - Does not address leachables in contact with inhalational drugs (Section 4.5).
  - If a medical device has already been evaluated as tissue contacting according to ISO 10993-1, then omission of testing for leachables per ISO 18562-4 may be considered (Section 5.4).
  - Risk estimation of allowable limits – references ISO 10993-17: Establishment of allowable limits for leachable substances (Section 7).
- **ISO 18562-2:** Assessments of emissions of particulate matter and allowable limits for particulates (<2.5-10 µM dia.), and methods of quantification.
- **ISO 18562-3:** Assessments of emissions of volatile organic compounds (VOCs) – max. flow rate and duration of use; quantification per ISO 16000-6; canisters per ASTM D5466.
- **ISO 18562-4**: Assessments of leachables in condensate
  - Assessments of leachables in liquid water (i.e., condensate) for devices that are intended to provide respiratory care.

Examples and Sources of Leachables

- **Examples of leachables:** Nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents

  https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf

- **Potential sources of leachables:** Chemical constituents used in the manufacturing process including base materials (e.g., polymerizers, solvents), additives (e.g., antioxidants, color additives), processing aids (e.g., lubricants, mold release agents), glues, sterilants (e.g., ethylene oxide)

  Norwood, Daniel, et al. "SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS ." SAFETY (2006): 4.

  https://scholar.google.com/scholar?q=pqri+safety+thresholds+and+best+practices+for+extractables+and+leachables&hl=en&as_sdt=0&as_vis=1&oi=scholart

- **Materials assessment:** Consider fitness of purpose, physical, mechanical, chemical and toxicological properties

18562-4: Assessing Leachables in Condensate

- Discusses use of best known science to address toxicological risks from potentially hazardous substances in condensate that are conveyed to the patient via GP. Condensate is distilled water from vapor phase.
- If the medical device under evaluation has already been evaluated as an indirect, external communicating medical device with contact to tissue/bone/dentin in accordance with ISO 10993-1, then [the suggested] leachables assessments need not be performed.
- Identify and quantify organic impurities using GC-MS or equivalent (Section 5.2(c)).

18562-4: Assessing Leachables in Condensate

To prepare a sample, either:

- produce and collect condensate under clinically relevant conditions, or
- circulate the water over the surface of the sample at a temperature representative of clinical use, or
- perform an aqueous extraction on the internal gas contacting surfaces in accordance with ISO 10993-12:2012, using clinically relevant conditions of temperature and duration.

For info on the extent and recognition of ISO 18562-4:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=36713

Deriving allowable limits: 18562-1, Section 7

For a chemical constituent detected through leachables assessment, determine maximum duration of exposure, and compare exposure values to:

1. Tolerable Intake (TI) : Obtain TI values from inhalational limits, or toxicity data.

   TI values factor in patient body weights (µg/kg) that covers the intended patient population.

   - If no TI to match exposure conditions, use modified TI per ISO 10993-17

2. Threshold of Toxicological Concern (TTC): Use TTC values if TI values cannot be derived.

   Defaults:

   - Acute exposure ≤ 24 hours: 360 µg/day
   - Prolonged exposure > 24 hours: < 30 days: 120 µg/day
   - Long term exposure ≥ 30 Days: 1.5 µg/day for each leachable or 40 µg/day for each Volatile Organic Compound (VOC)

Theoretical Leachables Analysis Using TI/TTC Values & Considerations

Substance	CAS#	Analytical Method (Not shown: Limit of Quantification)	Extraction Medium	Potential exposure/ Device (d)*	Default TTC *Based on exposure duration*
Bis (2-ethylhexyl) phthalate, DEHP	117-81-7 Derive TI	GC/MS	Pure water	**140 µg/d** *Acute*	360 µg/d *24 h* X
Theoretical	###-##-# If no TI, use TTC	GC/MS	Pure water	110 µg/d *Prolonged* ✓	120 µg/d *>24h, <30d*
Irganox 1076	2082-79-3	UPLC/MS	Pure water	*20 µg/d Prolonged* ✓	120 µg/d *>24h, <30d*
Benzoate derivative	?	GC/MS	Pure water	*20 µg/d Prolonged* ✓	120 µg/d *>24h, <30d*
Polyoxygenated unsaturated compounds	? Can't use TI	LC/MS	Pure water	**2.5 µg/d** ***Long term*** Needs ID & tox risk assmt.	1.5 µg/d *>30 d*

Tentative ID

*Sample calculation of amount per device: Concentration (µg/cm^2) x 200 cm^2 x (1 mg/1,000 µg) ÷ 3 devices

Setting TI values for carcinogenic leachables is discussed in ISO 10993-17

General Considerations on Best Practices

1. **A** toxicological risk assessment of leachables is dependent on chemical characterization approaches for identification (for determining a chemical constituent's toxicity) and concentration (for determining estimated exposure).
2. **I**dentifying materials of construction (identification of substances of chemicals of potential concern) is important for chemical characterization and establishing analytical methods needed to detect targeted compounds.
3. **U**nknowns and tentative identifications can affect the exposure limits that can be scientifically justified in a toxicological risk assessment.
4. **U**se qualified analytical methods for identifying and quantifying volatile, semi-volatile, non-volatile compounds (High Resolution GC/MS, LC/MS, UPLC/MS, ICP-MS) and metals (e.g., per USP <233>).

General Considerations on Best Practices

5. **P**rovide a justification that the Limit of Detection (LOD) of each analytical technique to demonstrate that the methods are capable of identifying and quantifying of leachables that will be used in the corresponding toxicological risk assessments.
6. **T**he chemical analysis provide the total quantity or amount (in weight) of identified chemical constituents per device.
7. **T**he toxicological risk assessment of the compounds detected within the chemical characterization takes into account the intended use of device and intended patient population (e.g. pediatric patients versus adults). For non-metals, refer to ISO 18562-1 and ISO 10993-17 for recommendations on allowable limits. For select metals, refer to USP <232> for allowable limits.

Guidances

- **Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators (OUTDATED)**
  https://www.fda.gov/RegulatoryInformation/Guidances/ucm081282.htm
- **Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations -Guidance for Industry (DRAFT)**
  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070573.pdf
- **Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation**
  https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf
- **Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories**
  https://www.fda.gov/combinationproducts/jurisdictionalinformation/jurisdictionalupdates/ucm103179.htm
- **Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"**
  https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Abbreviations

- CAS#: Chemical Abstracts Service #
- Dia: Diameter
- EC: Externally Communicating
- GC/MS: Gas Chromatography/Mass Spectrometry
- ICP-MS: Inductively Coupled Plasma Mass Spectrometry
- ISO: International Standards Organization
- LC/MS: Liquid Chromatography/Mass Spectrometry
- TI: Tolerable Intake
- TTC: Threshold of Toxicologic Concern
- UPLC/MS: Ultra-Performance Liquid Chromatography/Mass Spectrometry
- USP: United States Pharmacopeia
- VOCs: Volatile Organic Compounds

U.S. FOOD & DRUG ADMINISTRATION

US Food and Drug Administration + Devices

Thank you!