Review Considerations: Biocompatibility Assessment of Nasal Spray Devices

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FDA / CDRH / ODE / DAGRID / GHDB

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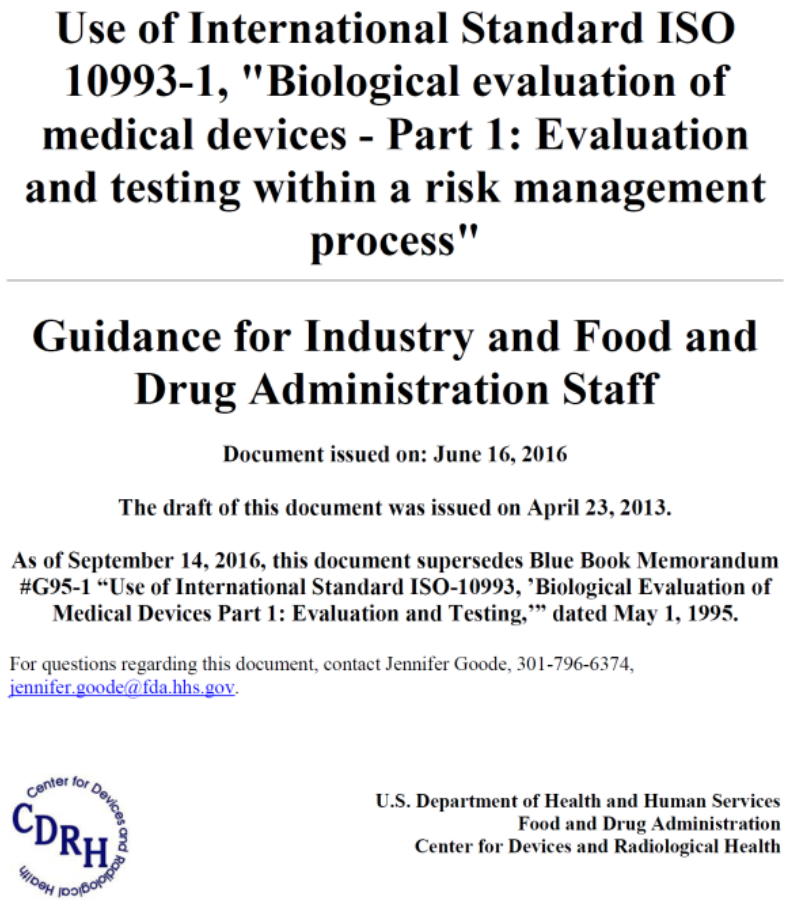
Agenda

- General Biocompatibility Considerations based on CDRH's 2016 Biocompatibility Guidance
- Combination Product/ Nasal Spray Biocompatibility Assessment
- Extractable/Leachable Considerations

When Biocompatibility is Considered

- As a critical part of FDA's determination of safety and effectiveness for:
  - **New devices:** if medical device materials come into direct or indirect contact with the human body
  - **Modified devices:** if changes are to direct or indirect contacting components (or could be)



Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Guidance for Industry and Food and Drug Administration Staff

Document issued on: June 16, 2016

The draft of this document was issued on April 23, 2013.

As of September 14, 2016, this document supersedes Blue Book Memorandum #G95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" dated May 1, 1995.

For questions regarding this document, contact Jennifer Goode, 301-796-6374, jennifer.goode@fda.hhs.gov.

Center for Devices and Radiological Health
CDRH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

How Biocompatibility is Considered

- For all submission types:
  - Device: PMA, HDE, IDE, 510(k), and De Novo requests
  - Device constituent of combination product: IND, NDA, BLA, ANDA
- To determine potential for unacceptable adverse biological response
- Biocompatibility standards can be used to facilitate information submission to FDA:
  - ISO 10993-1 and related 10993 series of standards
  - ASTM, ICH, OECD and USP biocompatibility standards

Risk Based Approach

- Per ISO 10993-1, includes consideration of:
  - Device design, material components and manufacturing processes
  - Clinical use of the device including the intended anatomical location
  - Frequency and duration of exposure
  - Potential risks from a biocompatibility perspective
  - Information available to address identified risks
  - Information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address risks

Risk Based Approach Continued

New biocompatibility testing may not be needed if both:

1. The device is made of materials that:
   - Have been well characterized chemically and physically in the published literature
   - Have been previously evaluated

2. Manufacturing and processing information support no new biocompatibility concerns.

Biocompatibility Evaluation: Sample Preparation

- Use device in its final, finished form (FFF)
  - e.g., sterile, if applicable
- Can leverage testing from previously evaluated device or a representative test article
  - Attachment F (example documentation language) may be helpful
- If not FFF, document any differences

Biocompatibility Evaluation: Sample Preparation

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

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Comparison to test article: "The test article is identical to the medical device in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)."

Comparison to previously marketed device: "The medical device in its final finished form is identical to **[name]** (previously marketed device) in formulation, processing, sterilization,

Biocompatibility Evaluation: Sample Preparation

- ISO 10993-12: details on sample preparation, for example:
  - Surface area/extract volume
  - Solvents: polar (e.g. saline) and non-polar (e.g. sesame or cottonseed oil) solvents
  - Extraction conditions (e.g. time and temperature)
- Simulation of extractables and leachables representative of clinical use conditions
- Extract separately:
  - Limited vs. prolonged vs. permanent components
  - Differences in contact type (e.g. intact skin vs externally-communicating)
  - New materials: assess separately from other material components

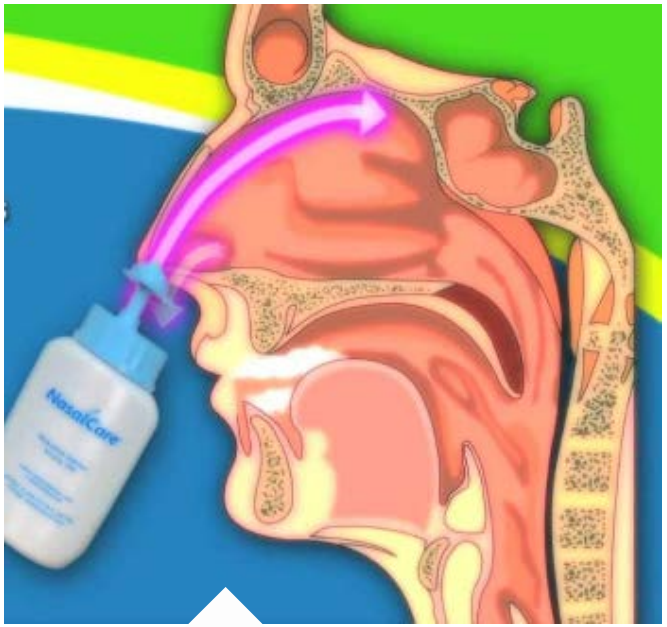
Biocompatibility Evaluation: Nasal Spray Devices

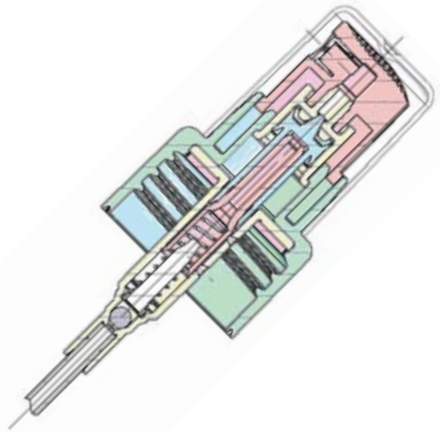
- Combination products
  - PMOA: drug (CDER lead)
  - CDRH consulted to review device performance
- Biological safety review
  - CDER: Primary container closure
  - **CDRH: device constituent(s) outside of primary container closure**

Contact Category and Duration

- **Direct contact:** term used for a device or device component that comes into physical contact with body tissue (e.g. cap or nozzle)

- **Indirect contact:** device or device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue (e.g. fluid path)





Contact Duration

- Multiple Scenarios for repeat use
  - Single-use device; multiple devices used over the course of treatment
  - Multi-use device; one device used over the course of treatment
  - Multi-use device; multiple devices used over the course of treatment
- Single-use device; one time or sporadic treatment

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Contact Duration

- Two separate considerations:
  - Cumulative exposure to patient used to determine contact duration (i.e. limited, prolonged, long-term)
  - Duration of contact of drug and fluid path used to determine extraction duration

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Nature of Contact

- **Direct contact:** e.g. cap or nozzle → Mucosal

- **Indirect contact:** e.g. fluid path) → blood path, indirect

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Nature of Contact

- **Direct contact:** e.g. cap or nozzle → Mucosal

- **Indirect contact:** e.g. fluid path) → blood path, indirect

Table 1. Modified FDA/CDER/CBER Risk-based Approach to Consideration of Leachables

Degree of concern associated with the route of administration	Likelihood of packaging component-dosage form interaction		
	High	Medium	Low
Highest	Inhalation aerosol and sprays	Injection and injectable suspension; inhalation solution	Sterile powders and powders for injection; inhalation powders
High	Transdermal ointment and patches	Ophthalmic solutions and suspension; nasal aerosol and sprays	
Low	Topic solutions and suspensions; topical and lingual aerosol; oral solutions and suspensions		Oral tablets and oral (hard and soft gelatin) capsules; topical powders; oral powders

Endpoint Evaluation

Table A.1: Biocompatibility Evaluation Endpoints

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		

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CDRH's 2016 Biocompatibility Guidance

Endpoint Evaluation

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Nature of Body Contact		Contact Duration 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 @
Category	Contact														
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		

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Endpoint Evaluation

Annex A
(informative)

Biological evaluation tests

Table A.1 is a framework for the development of an assessment program and is not a checklist (see Clause 6). For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in the Table A.1. In addition to the framework set out in Table A.1, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities.

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Hemocompatibility
Category	Contact									
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

ISO 10993-1: 2009

Contains Nonbinding Recommendations

Attachment A: Evaluation Endpoints for Consideration

The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. For particular medical devices, different biological endpoints may require evaluation, including either additional or fewer endpoints than indicated. If it is unclear in which category a device falls, we recommend consulting device-specific guidances or contacting the appropriate review division for more information.[63] For example, FDA has historically considered devices used to drain fluids (such as Foley catheters) as externally communicating devices rather than as surface devices contacting mucosal membranes.

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect													
Nature of Body Contact		Contact Duration 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@
Category	Contact														
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		

[63] Device categorization information can be obtained informally via email, or as a part of ODE's Pre-Submission process. Refer to FDA's guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff - Guidance for Industry and FDA Staff" (February 18, 2014).

CDRH's 2016 Biocompatibility Guidance

Endpoint Evaluation

X = ISO 10993-1:2009 asks for these.

O = CDRH also asks for these.

Address all **X**'s and **O**'s in the biological safety evaluation.

Use:

- Existing data,
- Additional endpoint-specific testing, or
- Rationale for why endpoint doesn't require additional assessment.

Endpoint Evaluation

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation															
Nature of body contact		Contact duration																
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity		Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/ developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/ bone/ dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant medical device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

[a] Refer to ISO 10993-11:2017, Annex F.

[b] Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.

[c] Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.

[d] If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment.

[e] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs.

[f] Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.

[g] X means prerequisite information needed for a risk assessment.

[h] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

[i] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.

[j] For all medical devices used in extracorporeal circuits.

ISO 10993-1:2018, Annex A (Table A.1) is much closer to Attachment A of CDRH's 2016 Biocompatibility Guidance, but there are still some important differences

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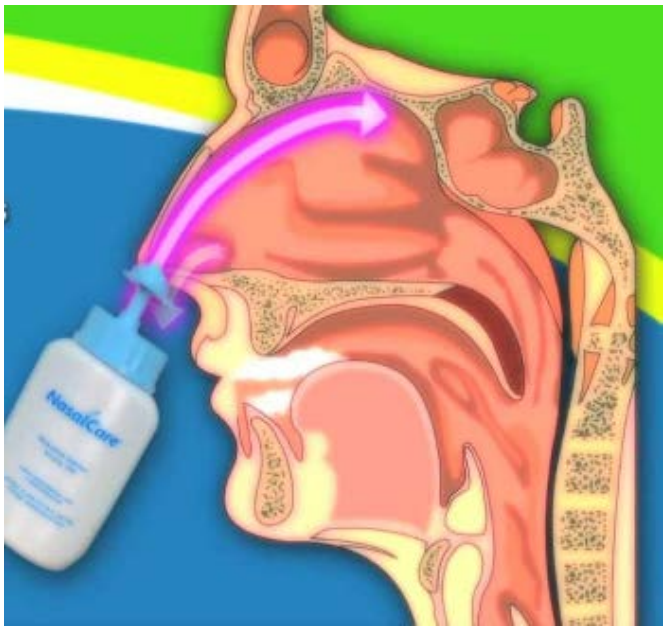
Endpoint Evaluation

- **Relevance:** All endpoints identified by an "X" or "O" in Attachment A* may not be relevant for all devices in a particular category
  - **Example:** Nasal Spray
    - Mucosal Membrane and blood-path, indirect
    - Prolonged contact
    - Implantation endpoint
    - Rationale: traditional subcutaneous/muscular implantation study (ISO 10993-6) not relevant based on how device is used



* of CDRH's 2016 Biocompatibility Guidance

Endpoint Evaluation

- **Novel materials/manufacturing processes:** Additional evaluations beyond those recommended in Attachment A* may be needed
- **Multiple types of exposure:** Include information to address each exposure category

* of CDRH's 2016 Biocompatibility Guidance

USP 87 vs ISO 10993-5

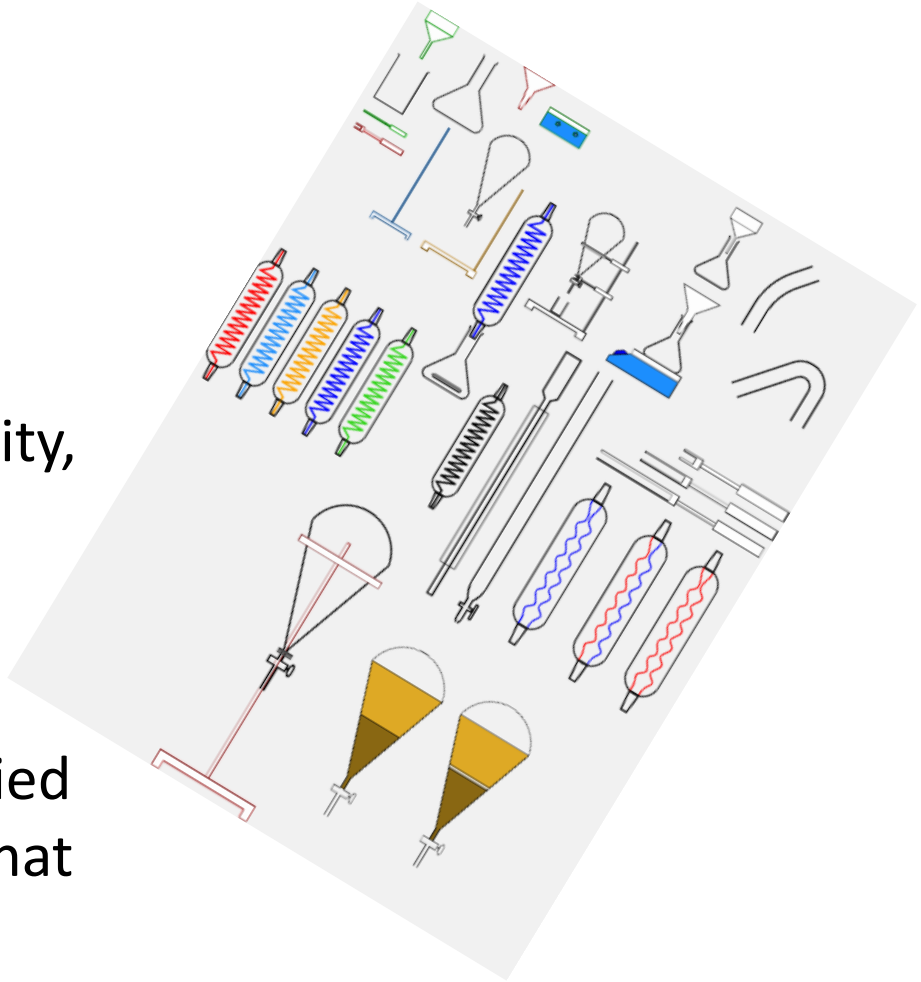
- The interpretation of the results are different from ISO 10993-5
- Consider any differences in the method used and how the results would still be acceptable per ISO 10993-5
- Provide test protocol and test report

USP 88 vs ISO 10993-1

- Endpoint selection is different than ISO 10993-1
- Sensitization is not included in USP 88
- The following parts of USP 88 are not recognized:
  - Page 171, Sentences, "Remove particulate matter, such as lint and free particles, by treating each subdivided Sample or Negative Control as follows. Place the Sample into a clean, glass-stoppered, 100-mL graduated cylinder of Type I glass, and add about 70 mL of Water for Injection. Agitate for about 30 s, and drain off the water. Repeat this step.“
  - Pages 174-175, Section "Safety Tests - Biologicals"

Extractables/Leachables Studies

- A chemical characterization and corresponding toxicological risk assessment can be used to:
  - address systemic toxicity endpoints (e.g. systemic toxicity, genotoxicity, carcinogenicity)
  - provide a comparison of previously studied and modified component to demonstrate that the type and quantity of chemicals are equivalent



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Extractables/Leachables Studies

- Exposure assessments:
  - Identity and amount of chemicals available to patients over time
  - Consideration of repeat device use
  - Extractables/leachables modeling or studies to optimize estimation of exposure during clinical use

- Safety assessments:
  - Known data from toxicology literature or material supplier
  - Derived Tolerable Intake (TI) or Threshold of Toxicological Concern (TTC) for unknowns, if TI cannot be derived

Extractables/Leachables Studies

- Extraction Studies to support safety assessments:
  - Polar solvents (e.g., water, physiological 0.9% saline)
  - Semi-polar solvents (e.g., isopropyl alcohol, ethyl alcohol, alcohol/water)
  - Non-polar solvents (e.g., hexane)
  - Extraction conditions (i.e., solvent, temperature, and duration) should not compromise device integrity

- Leachable Study or Simulated-Use Study to support safety assessments:
  - Specific drug product(s)
  - Drug product solvent

General Considerations: Extractables/Leachables Studies

- Consider worst case scenario for sample preparation for the Extractables/Leachables studies:
  - Exaggerative or exhaustive extraction conditions
  - ISO 10993-12 vs **LOQ**

- Test report(s):
  - the description of the test article
  - the extraction conditions utilized such as the polarity of test extractants, time and temperature
  - extraction ratio, the limit of quantification for analyses
  - test controls (e.g., reference standards), if used; and limitations of the evaluation)
  - justification for the solvents used based on the intended use of the device
  - Other relevant information

General Considerations: Extractables/Leachables Studies

- Analytical methods that can detect volatile, semi-volatile, non-volatile compounds as well as metals (i.e. GC/MS, LC/MS, and ICP-MS)
- The total quantity or amount (in weight) of all identified compounds per device
- Rationale for why the Limit of Quantification (LOQ) for the analysis is adequate for the intended use of the device
  - LOQ is an analytical threshold at or above which a chemist identifies and quantifies a particular extractable/leachable and reports it for potential toxicological risk assessment

General Considerations: Toxicological Risk Assessment

- Toxicological risk assessment of the compounds detected within the chemical characterization takes into account the intended use of device and intended patient population

- Some examples of items included in risk assessment reports:
  - a calculation of potential exposure to the patient
  - the results of a literature review of human and/or animal data on the toxicity of leachables and extractables
  - study end points
  - uncertainty or modifying factors related to the estimated dose extrapolation
  - a rationale for the acceptability of the TTC , if TTC values are used

Resources

- CDRH's 2016 Biocompatibility Guidance:

  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm348890.pdf

- Biocompatibility standards such as ISO 10993-1, and how CDRH uses them:

  www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Thank You!

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