CDRH Scientific Perspective on Chemical Analysis and Toxicological Risk Assessment for Medical Devices

Presenters: Berk Oktem, Alan Hood, Jennifer Goode

Co-authors: Eric Sussman, Samanthi Wickramasekara

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Objective

Discuss common analytical chemistry and toxicological risk assessment issues related to the 2016 CDRH Biocompatibility Guidance, ISO 10993-18 and ISO 10993-17.

Outline

1. Introduction: 21st Century Cures Act of 2016, least burdensome approaches
2. Background: Why Chemical Analysis and Toxicological Risk Assessment
3. Part I: Chemical Analysis Approaches
4. Part II: Toxicological Risk Assessment

Introduction

21st Century Cures Act -Section 3058: Least Burdensome Device Review

- CDRH Guidance :"The Least Burdensome Provisions: Concept and Principles" February 2019.
  - We define "least burdensome" to be the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time
  - The least burdensome provisions do not change the standards (i.e. level of information needed) for premarket approval or substantial equivalence
  - Least burdensome provisions form a 'two way street': "Industry should not submit information unrelated to the regulatory decision to FDA."

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Background: Why Chemical Analysis and Toxicological Risk Assessment

2016 CDRH Biocompatibility Guidance

- "potential risks from a biocompatibility perspective should be identified"
- "what information is already available regarding those risks and identify the knowledge gaps that remain"
- "address the knowledge gaps either by biocompatibility testing or other evaluations that appropriately address the risks"

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Background: Why Chemical Analysis and Toxicological Risk Assessment

2016 CDRH Biocompatibility Guidance

- "Inherent in the review of medical devices is an understanding of the body's entire exposure to the medical device, including all chemical entities contained within the device."

- "chemical analyses can be used to assess the toxicological risk of the chemicals that elute from devices. For example, chemical analysis using exhaustive extraction techniques (per ISO 10993-12) can also be helpful to evaluate long-term toxicity endpoints such as potential carcinogens…In addition, the outcomes of chemical analyses are often sensitive to the parameters of the test. Extraction solvents should be selected to optimize compatibility with the device materials "

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Background: Applicability of Other Industry Approaches

- Devices are not drugs
- Devices are not pharmaceutical packaging
- Devices are not food containers
- Analytical approaches that generate data adequate for toxicological risk assessment can be useful for medical devices

Material characterization of medical devices require unique approaches

Background: Brief Comparison of Different Industries

	Drug Products	Medical Devices
Contact	Until expiration date	1 minute to lifetime
Dose	Single, multiple or repeated	Single, multiple or repeated, continuously
Impurities identification	Leachables delivered with the drug product (tablet, liquid/solution)	Extractables released from the device components that contacts the body indirectly or directly.

Part I: Chemical Analysis Approaches

- Expanded Information in ISO FDIS 10993-18:2019
- Chemical Analysis: Purpose-Contact and other Considerations
- Considerations for Planning an Extraction Study and Analytical Tools
- Identification of Non-targeted Extractables
- Quantification and Reporting

Part I: Chemical Analysis Approaches

Non-targeted screening:

- Extraction: exhaustive or exaggerated extraction
- Data generation: multiple analytical methods
- Detect, identify and quantify: To provide data to support toxicological risk assessment

What Standards Are Used?

- A standardized method for complete chemical analysis of medical device materials does not currently exist.
  - CDRH partially recognizes ANSI AAMI BE83:2006/(R)2011 (there are differences between ISO 10993-18: 2005 and BE83)
  - CDRH does not recognize PQRI recommendations (2006)
- The "ISO FDIS 10993-18:2019 (recently balloted) includes additional details on analytical instruments, quantification methods, etc."

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm

Expanded Information in ISO FDIS 10993-18:2019

Concepts that do not appear in ISO 10993-18:2005

- AET: Analytical Evaluation Threshold, a pre-determined concentration above which an extractable is expected to be identified and semi-quantified.(definitions)
- The importance of identification (not new as concept but….)
- Expansion of reporting requirements

….and more

Analytical Evaluation Threshold: Reporting and Identification Limit

AET (µg/ml) = DBT (µg/day) x (A/(BxCxD)) ÷ UF

Dose-Based Threshold (DBT) = Threshold of Toxicological Concern (ICH M7)

A = number of medical devices extracted

B = extract volume

C = number of medical devices that contact the body

D** = dilution factor (D>1), if concentrated (D<1). If not diluted (D=1)

UF = uncertainty factor of analytical methods (UF >=1)

**D is optional: extract processing should be accounted for.

ISO FDIS 10993-18: 2019, Annex E

Analytical Evaluation Threshold: Reporting and Identification Limit

Device Contact Duration	DBT (µg/day)
Limited and prolonged (≤30 days)	120
Permanent/Long-term (>30 days)	1.5

Dose-Based Threshold (DBT) = Threshold of Toxicological Concern (ICH M7)

➡ **AET > LOQ , LOD**

Chemical Analysis Considerations

Common Questions:

- Purpose: what biocompatibility endpoints are addressed?
- Device Information
- Test Article Information
- Extraction
- Analysis
- Identification
- Quantification

Note: Chemical equivalency involves different considerations and will not be discussed today.

Purpose, Device and Test Article Information Considerations

- Purpose: to support biocompatibility evaluation of some biological endpoints (e.g., Acute Systemic Toxicity, Subacute/Subchronic Toxicity, Chronic Toxicity, Genotoxicity, Carcinogenicity)
- Device information: material list (direct and indirect contact)
- Test article information: final finished device, manufacturing considerations
- Information gathering: determine the scope of any analytical testing
- Extraction design: rationale for solvent selection, time/temperature of extraction, etc.

Analysis Considerations

	Duration of Contact		
	Limited (<24 h)	Prolonged (1-30 days)	Long-Term/ Permanent (>30 days)
Duration/ Number of Cycles	Exaggerated extractions or worst case clinically relevant conditions	Exhaustive extractions or worst case clinically relevant conditions	Exhaustive extractions
Number of solvents	Polar and non-polar solvents (or polar and mid-polar if justified)	Polar and non-polar solvents (or polar and mid-polar if justified)	Polar, mid-polar and non-polar
NVR Analysis Performed?	NVR analysis may be considered	NVR analysis to support if exhaustion is achieved	NVR analysis to support if exhaustion is achieved

System Suitability/Qualification

Establishing instrument sensitivity

- Following practices for robust method
  - 5 Point Calibration Curve
  - Use of internal standards
  - Use of more reference standards with varying response factors
- Selecting reference standards: Use of reference standards that match the expected/observed extractables can improve identification and quantification
  - Example:
    - Polyvinyl chloride (PVC): DEHP
    - Polyurethane: 4,4’-MDI

Considerations for Planning an Extraction Study and Analytical Tools

- Non-targeted vs. targeted methods
- Non-targeted (screening): detect, identify and semi-quantify extractables above AET
- Targeted: specific purpose (e.g. formaldehyde)
  - Could include specialized methods (e.g. 2,4 DNPH derivatization for carbonyl compounds)

Considerations for Planning an Extraction Study and Analytical Tools (cont.)

Comparison of equipment, temperatures:

- Closed vessel in temperature controlled incubator / shaker
  - Confirmation of agitation
  - Set temperature: e.g. 50 °C
- Soxhlet extraction
  - Losses of semi-volatiles, volatiles
  - Temperature variable depending on the boiling point of solvent
- Accelerated Solvent Extraction (ASE)
  - Not universal but may be applicable under certain conditions
  - Elevated temperature (up to 200°C) and pressure (1500psi)

Considerations for Planning an Extraction Study and Analytical Tools (cont.)

Time and temperature per ISO 10993-12 can be used as a starting point.

	Solvent	Polarity Index	Boiling point (°C)
Polar	Water	10.2	100
	Saline (0.9 % NaCl)	10.2	100
	Buffer: PBS, Tris etc.	10.2	100
Semi Polar	Dimethyl sulfoxide	7.2	189
	Acetonitrile	5.8	82
	Ethanol	4.3	78
	Tetrahydrofuran	4.0	65
	Isopropanol	3.9	82
	Dichloromethane	3.1	41
Non-Polar	Toluene	2.4	111
	Cyclohexane	0.2	81
	Hexane	0.1	69

ISO FDIS 10993-18:2019, Annex D

Considerations for Planning an Extraction Study and Analytical Tools (cont.)

Multiple methods to cover all types of chemicals:

- HS-GC-MS : volatile organic compounds (VOCs)
- GC-MS : semi-volatile organic compounds (SVOCs)
- LC-UV-MS: non-volatile organic compounds (NVOCs)
- LC-ELSD or CAD: non-volatile organic compounds (NVOCs)
- ICP-MS : Elemental analysis, metals
- FTIR, GPC, NMR, IC

Analytical instruments: selected to be fit for the intended purpose.

Considerations for Identification of Non-Targeted Extractables

- Purpose
- Identification Levels: confident or better?
- Identification Data: spectral library, supporting chemistry data, and expert judgement?

Example of a Tabulated Identification Assessment (TIA)

Name of Compound	CAS #	Extraction Vehicle	Analytical Instrument	Major Ions observed (m/z)	RT (min)	Identification level	Identification Data	Quantity (µg/device)	Quantification Method and reference standard
Diethyl phthalate	84-66-2	Hexane	GC/MS	279,167,149	6.2	Confirmed	Confirming Spectral library and RT match	10	Full-authentic reference std
Irgafos 168	31570-04-4	Ethanol	LC/MS	647.4608	7.25	Confident	Library match plus Supporting data	2	Semi-quantitative; Tinuvin P

Supporting data can include, but is not limited to, generation of a single molecular formula, matching retention time (RT), functional group data (e.g., UV), absence of possible alternative isomers, etc.

Considerations for Quantification

- Quantitative/semi-quantitative analysis
- Response factors
- Spike and recovery
- Duty cycle and ionization types
- AET for non-targeted extractables

Considerations for Reporting

- Information for toxicological risk assessment (TRA)
- Quantity in µg/device
- Comparison of Non-Volatile Residue (NVR) and total mass observed by all chemical methods
- 2016 CDRH Guidance has more (Section VII; Attachment E)….

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Part II. Toxicological Risk Assessment

- What is a toxicological risk assessment?
- Why conduct a toxicological risk assessment?
- When to consider toxicological risk assessment?
- Current Status of CDRH Recognition of ISO 10993-17:2002(R)2012
- Threshold of toxicological concern (TTC)
- Margin of Safety (MOS)
- How important is identification in toxicological risk assessment?
- Status of ISO TC 194 WG11 documents

What is a Toxicological Risk Assessment?

The act of determining the potential of a chemical/compound to elicit an adverse health effect based on a specified level of exposure

Toxicological Risk

Exposure Dose

Type	*Example*
External, internal, target site	*Extract concentration, Frequency, single/repeated*
Individual	*Adult (male/female), pediatric, infant/neonate*

+

Matching data = reduced uncertainty

Hazard

Type	*Example*
Adverse effect	*Animal/human (age/sex), treatment doses, single, repeated, frequency/duration*
Supporting information	*Chemical/physical, QSAR, in vitro, ADME, mechanism,*
Secondary source	*Peer review publication, non-peer review report*

Why Conduct a Toxicological Risk Assessment?

Can be useful for determining whether a chemical/compound present or released from a medical device presents a systemic toxic, genotoxic, carcinogenic reproductive, or developmental toxicological risk (other biological endpoints on a case-by-case basis).

"For devices where the patient-contacting portions may contain potentially toxic chemicals, the evaluation of safety should include both chemical risk (i.e., the level of toxicological concern) and the type and duration of exposure." – Section VII Chemical Assessment, page 42 of CDRH (2016) Biocompatibility Guidance

When to consider toxicological risk assessment?

When investigating presence/release of a chemical(s) of toxicological concern in a patient contacting material(s)

"*In addition, chemical analyses can be used to assess the toxicological risk of the chemicals that elute from devices.*" – Section B. Identification of Potential Risks, page 8, CDRH (2016) Biocompatibility Guidance

Note: "*However, chemical analysis is usually insufficient to identify all of the risks of the device in its final finished form, because it will not consider aspects of the finished device such as surface properties (e.g., rough versus polished surface) or device geometry that could affect the biological response in certain scenarios (e.g., thrombogenicity, implantation).*"

When to consider toxicological risk assessment?

When addressing a positive genotoxicity test result

"*In the event of a positive result, we recommend further investigation to identify the source of the genotoxin. We recommend this information be used to help evaluate the overall benefit-risk of the device using a toxicological risk assessment with respect to carcinogenicity, as described in Section VI.G, below.*" – Section F Genotoxicity, page 38, CDRH (2016) Biocompatibility Guidance

When to consider toxicological risk assessment?

- Devices made from novel materials (i.e., never before used in a legally US-marketed medical device)
- New chemicals used to modify material formulations or device manufacturing processes
- Devices made from chemicals with known toxicities (e.g., carcinogenicity), where new biocompatibility testing is rarely conducted
- Devices made from materials intended to change (e.g., in situ polymerizing or absorbable materials)
- Unexpected biocompatibility test findings
- "Long history of safe use" rationales

Per CDRH (2016) Biocompatibility Guidance, Section VII Chemical Assessment page 43

Current Status of CDRH Recognition of ISO 10993-17:2002(R)2012 – "Establishment of allowable limits for leachable substances"

Clause	Exclusions
1. Scope	
2. Normative references	
3. Terms and definitions	
4. General principles for establishing allowable limits	
5. Establishment of tolerable intake (TI) for specific leachable substances	
6. Calculation of tolerable exposure (TE)	Clause 6.2.1; Clause 6.3.2 b) 2) and Equation 6; Clause 6.3.3 and Equation 7
7. Feasibility evaluation	Clause 7.1 b) Paragraph 2 Clause 7.2, Words, either and or economically
8. Benefit evaluation	
9. Allowable limits	
10. Reporting requirements	
Annexes	Annex C, Clause C.2.1

Threshold of Toxicological Concern (TTC)

- ***"If data are not available to evaluate the safety of a compound, then the concept of Threshold of Toxicological Concern (TTC)[16] can be used to assess some biocompatibility endpoints."*** – Section C. Considering Available Information to Identify and Mitigate Risks 1 Literature and other publicly available information, page 9, CDRH (2016) Biocompatibility Guidance

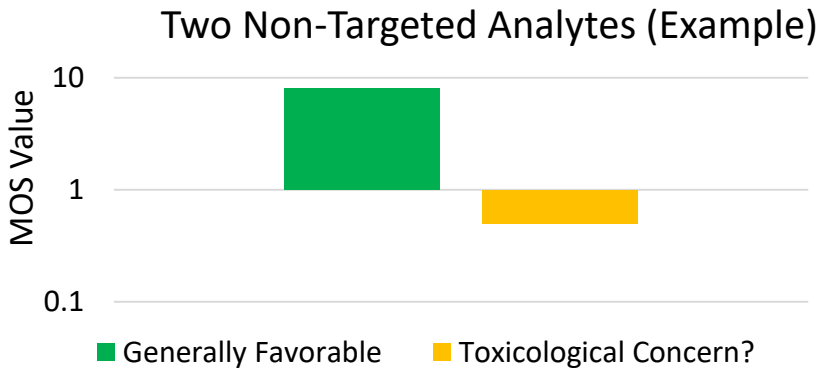
- ***"The TTC approach can be used to determine if quantification without chemical identification is sufficient to assess the toxicity risk of the device.[53] Otherwise, chemical identification is needed. "*** – Section G. Carcinogenicity, page 40, CDRH (2016) Biocompatibility Guidance

Margin of Safety (MOS)

Toxicological Threshold Dose ÷ **Dose**

- Threshold of Toxicological Concern (TTC) (ICH M7)
- Tolerable Intake (TI)/Point of Departure (POD)

- Amount present
- Total extractable amount
- Exposure estimate



Because MOS can be based on different types of toxicological and dose-based data, expert interpretation is used to derive and interpret MOS values

How important is identification in toxicological risk assessment of medical device extractables?

Background

- Textbook toxicological risk assessment method assumes identity of the chemical/compound of interest is known
- When screening for non-targeted extractables, identification of extractables can be challenging for the analytical chemist
  - Especially for extractables unexpected to be present
  - When spectra data of an unexpected analyte does not have a clear library match or no match at all

How important is identification in toxicological risk assessment of medical device extractables?

Background

- Analytical approaches for identifying a non-targeted extractable adequate for toxicological risk assessment is of interest in recent literature

- For medical device extractables, toxicological risk assessments is applied to extractables where molecular structure is elucidated to a confident/confirmed level, less-than-confident level, or not elucidated at all

How important is identification in toxicological risk assessment of medical device extractables?

Scope

Evaluate occurrence of reported MOS values based on identity (i.e., chemical molecular structure) and type of toxicological threshold

Selection Criteria

Submissions (*n*=6) received 2019, prolonged/long-term device contact, adult, non-targeted analysis, maximum exposure dose estimate

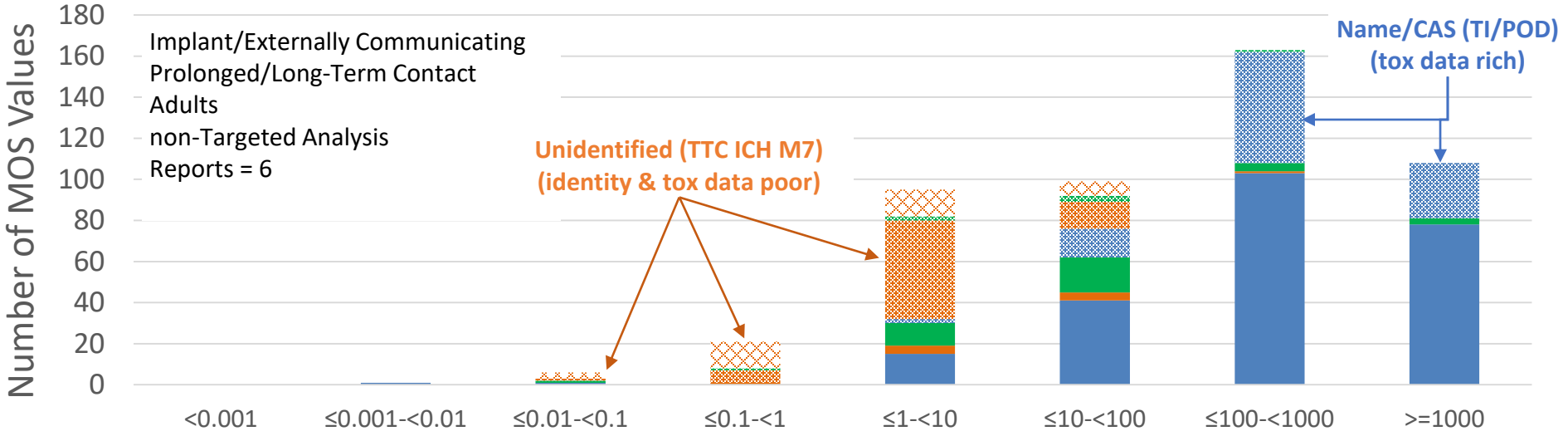
How important is identification in toxicological risk assessment of medical device extractables?

Summary of Reported MOS values

	Molecular Structure	Total
MOS Values	N/A	529
Names/CAS #'s	Complete	191
Other	Incomplete	125
Unidentified	Absent	11

Grouping Reported MOS Values by Identity

Note: Data does not imply risk assessment outcome



Toxicity data rich

- Name/CAS # TI (POD)
- Other TI (POD)

Toxicity data poor

(Suspected mutagenic carcinogen)

- Name/CAS # TTC (ICH M7)
- Other TTC (ICH M7)
- Unidentified TTC (ICH M7)

Toxicity data poor

(Suspected systemic toxicant)

- Name/CAS # TTC (Cramer Class)
- Other TTC (Cramer Class)
- Unidentified TTC (Cramer Class)

Grouping Reported MOS Values by Identity

Summary/Conclusion

>1 MOS values:

almost always occur when complete molecular structure and TI/POD are reported

<1 MOS values:

almost always occur when absence of molecular structure and TTC are reported

Medical device MOS values evaluated support identification is important when assessing whether a non-targeted extractable will not raise a toxicological concern without potential need for additional justification

ISO TC 194 10993 Standards

ISO Technical Specification (TS) 21726 "Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents"

- Published by ISO in February 2019
- Currently under review by CDRH for status of recognition
- Recognition will be published at FDA Recognized Consensus Standards database https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

ISO TC 194 10993 Standards (cont.)

ISO 10993-7:2008/DAM 1:2018(E) “Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals”

- Comments resolved in ISO TC 194 WG11 meeting in Berlin
- Draft amendment with resolved comments sent to Secretariat for balloting

ISO TC 194 10993 Standards (cont.)

New Work Item Proposal (NWIP) to revise ISO 10993-7 "Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals"

- Initiating NWIP
- Working draft (WD) to begin in 2019
- Initial discussion of WD at next ISO TC 194 WG11 meeting

ISO TC 194 10993 Standards (cont.)

Revision of ISO Biological evaluation of medical devices— Part 17: "Toxicological risk assessment of medical device constituents"

- ISO TC 194 WG11 Writing Team is creating working draft (WD)
- WD to be balloted June/July 2019
- WD to be discussed at next ISO TC 194 WG11 meeting (Q4 2019, Arlington, VA)

ISO TC 194 10993 Standards (cont.)
ISO 10993-17 Current (2002(R)2012) vs Working Draft

Current	Working Draft (WD)
ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances	**ISO WD 10993-17 (current) Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents**
1. Scope	1. Scope
2. Normative references	2. Normative references
3. Terms and definitions	3. Terms and definitions
4. General principles for establishing allowable limits	4. Overview of toxicological risk assessment within the biological evaluation process
5. Establishment of tolerable intake (TI) for specific leachable substances	5. Planning and scoping
6. Calculation of tolerable exposure (TE)	6. Hazard identification
7. Feasibility evaluation	7. Dose-response assessment
8. Benefit evaluation	8. Exposure assessment
9. Allowable limits	9. Risk characterization
10. Reporting requirements	10. Risk control
	11. Reporting requirements

Contacting CDRH

a) Pre-submission

https://www.fda.gov/media/114034/download

b) Technical Contacts on Guidance Documents

c) Recognized Consensus Standards

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

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- Society of Toxicology, Medical Device and Combination Products Specialty Section for hosting this event

* 5/1/2019 reorganization combined Office of Device Evaluation (ODE), Office of Compliance (OC) & Office of Surveillance and Biometrics (OSB)

Thank you!

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Supplemental Information

ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition

(Recognition Number 2-237, July 26, 2016)

Clause 6 Calculation of Tolerable Exposure (TE)

6.2 Exposure population

6.2.1 Body mass

The bulk of medical devices are used in adults. Thus 70 kg shall be used to calculate TE unless the device is intended for use in another population. In that case, the TE shall be based on the body mass derived from the dominant use pattern, with special consideration given to devices specifically intended for use with uniquely sensitive groups, such as neonates. See annex A for a variety of body masses that may be used.

Supplemental Information

ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition (Recognition Number 2-237, July 26, 2016)

6.3.2 Concomitant exposure factor (CEF)

Assess the extent of exposure to a specific leachable substance arising from the use of multiple devices. Determine a concomitant exposure factor (CEF) of between 0.2 and 1.0 on the basis of this assessment, in line with the following principles.

a) Use a CEF of 0.2 if the utilization factor is unknown.

b) If many medical devices (i.e., at least 5 % of the devices sold in a calendar year, or more than five devices in any single medical procedure) can release the leachable substance, the CEF shall be calculated as either:

1) the product of TI and body mass (m_B) divided by the total amount of leachable substance expected to be released by medical devices during a procedure as given in equation (5), or

$$CEF = \frac{TI \cdot m_B}{m_{proc}} \quad (5)$$

where

TI is the tolerable intake, in milligrams per kilogram body mass per day;

m_B is the body mass, in kilograms;

m_{proc} is the mass of total leachable substance released during a procedure, in milligrams per day.

2) the product of TI and m_B divided by the anticipated mean daily exposure of an average person to the leachable substance from all devices over a lifetime as given in equation (6), or

$$CEF = \frac{TI \cdot m_B}{\sum \frac{m_{life}}{25{,}000 \text{ days}}} \quad (6)$$

Supplemental Information
ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition
(Recognition Number 2-237, July 26, 2016)

6.3.3 Proportional exposure factor (PEF)

A utilization factor (UTF) can be adjusted upwards to account for a situation where a device is not used for the entire duration of an exposure category. To facilitate this, a proportional exposure factor (PEF) shall be calculated as the proportion of the exposure category during which actual exposure to the device is anticipated to occur. Thus, as shown in equation (7), the PEF equals the number of days in the exposure category divided by the number of days a device is used before it is discarded.

$$PEF = \frac{n_{exp}}{n_{use}} \quad (7)$$

where

n_{exp} is the number of days in the exposure category;

n_{use} is the number of days of device use.

If the number of days a device is used varies, a reasonable upper limit should be used. If a reasonable upper limit can not be determined, use a PEF default of 1.

Supplemental Information

ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition

(Recognition Number 2-237, July 26, 2016)

7 Feasibility evaluation

7.1 Feasibility refers to the ability of a manufacturer or reprocessor to achieve the tolerable exposure. Feasibility has two components:

a) technical feasibility; and

b) economic feasibility.

Technical feasibility refers to the ability to achieve the tolerable exposure for a device or device class regardless of cost.

Economic feasibility refers to the ability to meet the tolerable exposure without making provision of the device an unsound economic proposition. Cost and availability implications should be considered in the selection of allowable limits to the extent that these impact upon the preservation, promotion or improvement of human health.

Supplemental Information

ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition

(Recognition Number 2-237, July 26, 2016)

7.2 If achieving the tolerable exposure is feasible, benefit evaluation shall not be performed, the benefit factor defaults to 1 and the allowable limit is the same as the tolerable exposure. If it is either technically or economically infeasible to meet the tolerable exposure, benefit evaluation should be performed. The rationale for the consideration of benefit should be documented.

Supplemental Information

ISO 10993-17:2002(R)2012 Clauses Excluded from CDRH Recognition

(Recognition Number 2-237, July 26, 2016)

Annex C (informative) Conversion of allowable limits for systemic exposure and for body surface contact to maximum dose to patient from a medical device

C.2 Calculation of the maximum dose to patient of a leachable substance from a medical device for systemic exposure

C.2.1 Permanent-contact devices

Medical devices in the permanent-exposure category may be used from 31 days to 25,000 days.

The formula for calculation of the maximum amount of a substance that may be leached from a medical device in the permanent-exposure category follows:

$$m_{dev,\ perm} = AL_{perm} \times 25{,}000 \qquad (C.1)$$

where

$m_{dev,\ perm}$ is the maximum amount per device, i.e. maximum dose to patient in milligrams;

AL_{perm} is the allowable limit for the permanent-exposure category, in milligrams per day.