# Biocompatibility Evaluation of Ophthalmic Medical Devices

**Simona Bancos, Ph.D.**
Center for Devices and Radiological Health (CDRH)
Office of Health Technology 1
Division of Ophthalmic Devices

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# Presentation outline

- Examples of ophthalmic devices
- When biocompatibility is considered
- Biocompatibility-relevant FDA guidance documents and FDA-recognized standards for ophthalmic devices
- Overview of CDRH's 2016 Biocompatibility Guidance
- Key changes to ISO 10993-1:2018 from prior versions of the standard
- Important risk-based considerations
- How chemistry information is used in biocompatibility evaluations

# Key Definitions*

- Biocompatibility: ability of a device material to perform with an appropriate host response in a specific situation
- Direct contact: term used for a device or device component that comes into physical contact with body tissue
- 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 (in this case the device or device component itself does not physically contact body tissue)

*CDRH's 2016 Biocompatibility Guidance: https://www.fda.gov/media/85865/download

# Key Definitions* (continued)

- Final finished form: term used for a device or device component that includes all manufacturing processes for the “to be marketed” device including packaging and sterilization, if applicable
- Novel material: material that has not previously been used in any legally US-marketed medical device

*CDRH’s 2016 Biocompatibility Guidance

# Examples of ophthalmic devices

U.S. FOOD & DRUG ADMINISTRATION

**Therapeutic**

Contact lenses and Contact lens care products

**Prosthetic**

Keratoprosthesis, Intraocular lenses (IOL), Aqueous shunts

**Diagnostic**

Ophthalmic camera, Ophthalmoscope, Tonometers

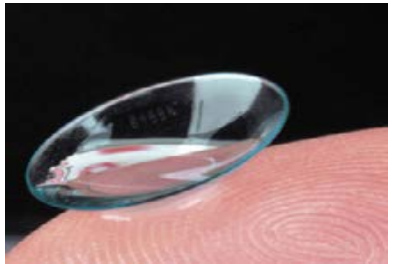
**Surgical**

Phacophragmentation systems, IOL guide, Intraocular gas

# Risk-based Paradigm[1]

## Sunglasses

## Contact lenses



## Intraocular lenses

| Class I | Class II | Class III |
|---|---|---|
| Low risk | Moderate risk | Highest risk |
| Most exempt from premarket submission | Premarket notification [510(k)] | Premarket Approval Application (PMA) |

[1]http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/

# When Biocompatibility is Considered

- For all devices with direct and indirect patient contact component
- For new devices or changes to devices/device components with direct and indirect patient contact
- For all submission types: PMA, Humanitarian Device Exemption (HDE), Investigational Device Exemption (IDE), 510(k), and De Novo requests

# How Biocompatibility is Considered

- Use of FDA guidance documents and FDA-recognized standards is recommended to facilitate information submission to FDA

- Existing FDA guidance documents and standards for ophthalmic devices provide considerations for recommended biological evaluation and testing

# FDA Guidance Document

- Describes FDA's interpretation of, or policy on, a regulatory issue
- Search for FDA Guidance Documents using the database on FDA website*

*Example of a search for CDRH guidance documents using "ophthalmic" as a keyword*

**Search**

ophthalmic

Showing 11 to 13 of 13 entries (filtered from 681 total entries)

**Filters**

Export Excel | Show 10 entries

| Summary | Document | Issue date | Topic | Guidance Status | Open for Comment | Comment Closing Date on Draft | Docket Number |
|---|---|---|---|---|---|---|---|
| Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices | PDF (418.97 KB) | 08/17/2015 | Premarket, Medical Devices, Ophthalmic | Final | No | | FDA-2014-D-0332 |
| Premarket Notification 510(k) Guidance for Contact Lens Care Products | PDF (359.53 KB) | 05/01/1997 | Premarket, 510(k), Medical Devices, Ophthalmic | Final | No | | |
| Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses (Part 5) | PDF (1.58 MB) | 06/28/1994 | Premarket, 510(k), Medical Devices, Ophthalmic | Final | No | | |

* https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch

# FDA Guidance Documents for Ophthalmic Devices

(not a comprehensive list)

- Guidance Document for Class II Daily Wear Contact Lenses (1994)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-notification-510k-guidance-document-class-ii-daily-wear-contact-lenses
- Guidance Document for Contact Lens Solution and Care Products (1997)
  https://www.fda.gov/media/72725/download
- Aqueous Shunts-510(k) Submissions-Guidance for Industry and for FDA Reviewers/Staff (1998)
  https://www.fda.gov/media/71885/download

# FDA Guidance Documents for Ophthalmic Devices (cont.)

(not a comprehensive list)

- Guidance on 510(k) Submissions for Keratoprostheses-Guidance for Industry and for FDA Reviewers/Staff (1999)
  https://www.fda.gov/media/71810/download
- Guidance Document for Minimally Invasive Glaucoma Surgical (MIGS) Devices (2015)
  https://www.fda.gov/media/90950/download

# FDA-recognized voluntary consensus standards

- The term “recognize” or “recognition” is defined in Section 514c of the Food, Drug, and Cosmetic Act
- “Recognize” refers to FDA’s identification of standards as appropriate for manufacturers of medical devices to declare conformance or to use the standard in a submission or other aspect to satisfy a requirement
- The extent of recognition varies:
  - Full recognition
  - Partial recognition

# Search for FDA-Recognized Consensus Standards


*Search for standards on the FDA website using the designation number and/or a keyword*

https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch

# Search for FDA-Recognized Consensus Standards (cont.)

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New Search | Back To Search Results

**Part B: Supplementary Information Sheet (SIS)**

**FR Recognition List Number** 018 **Date of Recognition** 09/12/2007

**FR Recognition Number** 10-48

**Standard**

ISO 11979-5 Second edition 2006-06-01
Ophthalmic implants - Intraocular lenses - Part 5: Biocompatibility

**Scope/Abstract**

This part of ISO 11979 specifies particular requirements for the biocompatibility evaluation of materials for intraocular lenses (IOLs) including the processing conditions to produce them. These requirements include evaluation of physicochemical properties that are relevant to biocompatibility. It also gives guidance on conducting an ocular implantation test.

**Extent of Recognition**

Complete standard

**Rationale for Recognition**

This standard is relevant to medical devices and is recognized on its scientific and technical merit and/or because it supports existing regulatory policies.

**Public Law, CFR Citation(s) and Procode(s)**

| Regulation Number | Device Name | Device Class | Product Code |
|---|---|---|---|
| §886.3600 | Intraocular Lens | Class 3 | HQL |
| §886.3600 | Lens, Intraocular, Accommodative | Class 3 | NAA |
| §886.3600 | Lens, Intraocular, Toric Optics | Class 3 | MJP |
| §886.3600 | Lens, Iris Reconstruction | Class 3 | NIZ |
| §886.3600 | Lens, Multifocal Intraocular | Class 3 | MFK |

**Relevant FDA Guidance and/or Supportive Publications**

There is no relevant guidance developed at this time.

**FDA Technical Contact**

**Simona Bancos**
FDA/OMPT/CDRH/ODE/DOED/ICIB/
301-796-6860
simona.bancos@fda.hhs.gov

**Standards Development Organization**

ISO International Organization for Standardization https://www.iso.org/

**FDA Specialty Task Group (STG)**

Ophthalmic

# FDA-Recognized Consensus Standards for Ophthalmic Devices

(not a comprehensive list)

- ISO 11979-5 (Second edition, 2006): Ophthalmic implants-Intraocular lenses - Part 5: Biocompatibility
- ISO 9394 (Third edition, 2012): Ophthalmic optics- Contact lenses and contact lens care products - Determination of biocompatibility by ocular study with rabbit eyes
- ISO 15798 (Third edition 2013, Amended 2017): Ophthalmic implants - Ophthalmic viscosurgical devices
- ANSI Z80.27-2014 American National Standard for Ophthalmics - Implantable Glaucoma Devices
- ISO 18189 (First edition, 2016): Ophthalmic optics – Contact lenses and contact lens care products - Cytotoxicity testing of contact lenses in combination with lens care solution to evaluate lens/solution interactions

# Contact Lens Biocompatibility
## (Guidance Document for Class II Daily Wear Contact Lenses,1994)

- Minimum recommended biocompatibility test for Class II Contact Lenses:
  - Cytotoxicity
  - Systemic toxicity
  - Ocular Irritation
- The tests recommended for packaging materials

# Contact Lens Biocompatibility
## (Guidance Document for Class II Daily Wear Contact Lenses,1994)

- Additional biocompatibility tests:
  - If a lens material is manufactured using a new monomer or an UV-absorber is incorporated which has not been cleared previously for same class of lenses using the same method of incorporation into the lens marketed by the manufacturer:

    - Sensitization test
    - Three week ocular irritation study in rabbits

# Intraocular Lens Biocompatibility (ISO 11979-5)

- Biocompatibility Testing:
  - Cytotoxicity
  - Sensitization
  - Genotoxicity
  - Local Effects after Implantation
  - Ocular Implantation Study

# Intraocular Lens Biocompatibility (ISO 11979-5; cont.)

- Physicochemical Testing:
  - Exhaustive Extraction
  - Leachables
  - Hydrolytic Stability
  - Photostability against UV/Vis irradiation
  - Neodymium-doped Yttrium Aluminium Garnet (Nd-YAG) Laser Exposure
  - Insoluble Inorganics

# Summary I

- Biocompatibility assessed for all devices with direct and indirect patient contact
- Biocompatibility assessment performed per FDA-guidance documents and FDA-recognized standards for the specific device

# Summary I (cont.)

- Available FDA guidance and FDA-recognized standard documents are available for:

  - Contact lenses and contact lens care products
  - Intraocular lenses
  - Aqueous shunts
  - Minimally invasive glaucoma surgical devices
  - Keratoprostheses
  - Viscosurgical devices

# CDRH's 2016 Biocompatibility Guidance

## 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.

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

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

# CDRH's 2016 Biocompatibility Guidance (cont.)

- How FDA uses International Standard Organization (ISO) 10993-1 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"

- Focus:

  *How to use risk management to:*
  *1) Address biocompatibility, and*
  *2) Leverage existing testing, if possible*

Instead of: What biocompatibility testing is needed?

# ISO 10993-1: 2018

FDA U.S. FOOD & DRUG ADMINISTRATION



INTERNATIONAL STANDARD

**ISO**

**10993-1**

Fifth edition
2018-08
Corrected version
2018-10

**Biological evaluation of medical devices —**

Part 1: **Evaluation and testing within a risk management process**

*Évaluation biologique des dispositifs médicaux —*
*Partie 1: Évaluation et essais au sein d'un processus de gestion du risque*

# ISO 10993-1: 2018 (cont.)

- Fifth edition published: Aug-2018 (corrected: Oct-2018)
- The current edition contains revisions on:
  - New/revised definitions (Clauses 3.1 through 3.26)
  - New information on:
    - Non-contacting (Clause 5.2.1) & transitory-contacting (Clause 5.3.2) medical devices
    - Nanomaterials & absorbable materials

# ISO 10993-1: 2018 (cont.)

- Fifth edition published: Aug-2018 (corrected: Oct-2018)
- As compared to the Fourth edition, the current edition contains revisions on:
  - New/revised definitions (Clauses 3.1 through 3.26)
  - New information on:
    - Non-contacting (Clause 5.2.1) & transitory-contacting (Clause 5.3.2) medical devices
    - Nanomaterials & absorbable materials

This content is recognized by CDRH

# ISO 10993-1: 2018 (cont.)

- Revised Annex A

  This content is PARTIALLY recognized by CDRH

- Revised Annex B (to incorporate Technical Report (TR) 15499 Guidance)

  This content is recognized by CDRH

# Key Changes to ISO 10993-1: 2018

- New information on Nanomaterials (not a comprehensive list):
  - Medical devices that contain, generate, or are composed of nanomaterials can pose specific challenges to the biological evaluation due to their potentially unique properties
  - Nanomaterials can pose specific challenges (e.g., assay interference)
  - Material characterization for nanomaterials conducted per ISO/TR 10993-22

# Key Changes to ISO 10993-1: 2018 (cont.)

- Revised information on Absorbables (not a comprehensive list):
  - If a medical device is intended to change during its lifetime, such as those that are polymerized and/or degraded in situ, the evaluation shall consider all the different device states

# Key Changes to ISO 10993-1: 2018 (cont.)

- Revised information on Absorbables (not a comprehensive list):
  - Degradation tests shall be considered if the medical device is designed to be absorbable
  - In vivo degradation tests might not be necessary if an in vitro/in vivo comparison for the absorbable medical device has been previously demonstrated

# ISO 10993-1: 2018, Annex A, Table A.1

- New title: "**Endpoints** to be addressed in a biological risk assessment"
- New column: **physical and/or chemical information**
- New column: **material mediated pyrogenicity**
- Column reinstated: chronic toxicity
- Column reinstated: carcinogenicity
- Column reinstated: reproductive/developmental toxicity
- Column reinstated: degradation
- **E (endpoints to consider)** instead of X (tests to conduct)

This content is PARTIALLY recognized by CDRH. CDRH does not recognize Table A.1

# ISO 10993-1: 2018, Annex A (cont.)

## Annex A
(informative)

## Endpoints to be addressed in a biological risk assessment

### A.1 General

The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. Where Table A.1 indicates that an endpoint is relevant for assessment, the existing data sets relevant to that endpoint should be evaluated to determine if any additional data sets are needed. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

In Table A.1; X means prerequisite information needed for a risk assessment; 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 assessment)

Any variation should be justified in the biological risk assessment. If there are device specific standards that include specific recommendations regarding biocompatibility, these should be considered.

This content is recognized by CDRH

# ISO 10993-1: 2018, Annex A (cont.)

- Key recommendations in Annex A:
  - "not a checklist for testing"
  - "there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated"
  - "X means prerequisite information needed for a risk assessment"

This content is recognized by CDRH

# ISO 10993-1: 2018, Annex A (cont.)

- Key recommendations in Annex A:
  - "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 assessment"

This content is recognized by CDRH

# ISO 10993-1: 2018, Annex A (cont.)

- Key recommendations in Annex A:
  - "Any variation should be justified in the biological risk assessment"
  - "Device specific standards… should be considered"

This content is recognized by CDRH

# ISO 10993-1: 2018, Annex A (cont.)

- Table A.1:  different endpoints are recommended for evaluation in the 2018 revision (as compared to the 2009 version of ISO 10993-1)

- Table A.1 not recognized by CDRH

# ISO 10993-1: 2018, Annex A (cont.)

Table A.1 NOT recognized by CDRH – see 2016 CDRH Biocomp Guidance Attachment A

**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 | Sensitization | 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 | | | |

✓ = consistent w/2016 Guidance; ⊘ = not consistent w/2016 Guidance

# ISO 10993-1: 2018, Annex A (cont.)

Table A.1 NOT recognized by CDRH – see 2016 CDRH Biocomp Guidance Attachment A

| 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 | Sensitization | 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] |
| 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.

✓ = consistent w/2016 Guidance; ⊘ = not consistent w/2016 Guidance

# ISO 10993-1: 2018, Annex A (cont.)

- Clause A.2 explains why the endpoints included in Table A.1 have changed
- Clause A.2 is recognized by CDRH

This content is recognized by CDRH

# 10993-1:2018, Annex A (cont.)

- Clause 4.1 (last paragraph): "Evaluation can include both a review of relevant existing preclinical and clinical data and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the medical device under design."

This content is recognized by CDRH

# Back to the 2016 CDRH Biocompatibility Guidance

# When Biocompatibility is Considered

- For all devices with direct and indirect patient contact component
- For new devices or changes to devices/device components with direct and indirect patient contact
- For all submission types: PMA, HDE, IDE, 510(k), and De Novo requests

# 2016 CDRH BIOCOMPATIBILITY GUIDANCE

U.S. FOOD & DRUG ADMINISTRATION

## 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 | | | | | | | | | | | | | |
| 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 | | |

[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).

**NOTE: X/O marks are relevant to 2009 version of ISO 10993-1**

This content PARTIALLY consistent with 10993-1:2018

# Endpoint Assessment vs. Testing (cont.)

- 2016 CDRH guidance recommends that all endpoints marked with “X” and “O” be considered

- To address all “X” and “O” endpoints sponsors can use:
  - Existing data,
  - Additional endpoint-specific testing, or
  - Rationale for why endpoint doesn’t require additional assessment

This content is consistent with 10993-1:2018

# Endpoint Assessment vs. Testing (cont.)

- **Relevance:** All endpoints identified by an "X" or "O" in Attachment A of 2016 Guidance may not be relevant for all devices in a particular category
- **Novel materials/manufacturing processes:** Additional evaluations beyond those recommended in Attachment A of 2016 Guidance may be needed
- **Multiple types of exposure:** Include information to address each exposure category

This content consistent with 10993-1:2018

# Sample Preparation

**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 Me cal 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.

**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,

This content consistent with 10993-1:2018

# 2016 FDA Guidance Recommendations for Chemistry Information

- In additional to biocompatibility testing, chemistry information may be requested
- Chemistry information may include descriptive information and/or chemical testing

This content consistent with 10993-1:2018

# 2016 FDA Guidance Recommendations for Chemistry Information (cont.)

- Examples when FDA may request additional chemistry information (not a comprehensive list):
  - Devices made from materials intended to change (e.g., in situ polymerizing or absorbable materials)
  - Devices made from chemicals with known toxicities (e.g., carcinogenicity), where new biocompatibility testing is rarely conducted
  - Devices made from novel materials

This content consistent with 10993-1:2018

# 2016 FDA Guidance Recommendations for Chemistry Information (cont.)

- Descriptive information can include:
  - Chemical identity
  - Composition, formula/formula weight, structural information, manufacturing and purity information
  - Amount by weight percent and total amount (e.g., µg)
  - Identity of other US marketed devices with same chemical

This content consistent with 10993-1:2018

# 2016 FDA Guidance Recommendations for Chemistry Information (cont.)

- To evaluate the patient exposure to the device/ device component chemical(s), exposure information may be provided

- Exposure assessments may include:

  - Chemicals and related impurities that may be available over time
  - Consideration of repeat device use
  - Extractables/leachables modeling or studies to optimize estimation of exposure during clinical use

This content consistent with 10993-1:2018

# 2016 FDA Guidance Recommendations for Chemistry Information (cont.)

- To evaluate the patient exposure to the device/ device component chemical(s), safety assessments may be provided

- Safety assessments may include:

  - 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

This content consistent with 10993-1:2018

# Summary II

- Use recommendations of 2016 CDRH Biocompatibility Guidance for ophthalmic devices that do not have a specific FDA guidance and/or FDA-recognized standard document
- Biocompatibility assessment needed for changes to devices with direct and indirect patient contact
- Use Attachment A of the 2016 CDRH Biocompatibility Guidance when considering endpoint assessments for CDRH submissions (instead of ISO 10993-1:2018, Table A.1)

# Summary II (cont.)

- Attachment A of the 2016 CDRH Biocompatibility Guidance may not be relevant for all devices in a particular category
- Additional evaluations beyond those recommended in Attachment A may be needed
- “Chemistry information” does not always require analytical chemistry testing
- ISO 10993-1:2018 revisions are consistent with the 2016 CDRH Biocompatibility Guidance (except Table A.1 in Annex A)