The Testing and Risk Management Impacts of Changing a Medical Device

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What Constitutes a Change?

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Why are you changing?

- Any change needs an evaluation….any change.
- If you change your device with the **intent** to significantly affect the safety or effectiveness of the device, more in-depth evaluation including new 510k may be needed.
- What about…
  - Label changes
  - Packaging
  - Materials/process changes
  - Adding a colorant (https://www.nelsonlabs.com/events/changing-a-colorant-in-an-approved-medical-device-what-should-i-know/)
  - Location change

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First Step: Risk Assessment

First step to any change is an initial risk assessment

- Is the change impacting a patient contacting material? Only intact skin?
- Is the intent of the change to significantly improve clinical outcomes?
- Is it to mitigate a known risk?
- Are there any unintended consequences of changes?
- What testing should be done to mitigate any risks?

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Example of Mitigating the Risk of Safety

What is **Risk**?

ISO 14971 Definition: Combination of the **probability of occurrence** of harm and the **severity of that harm.**

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

Section III. Risk Management for Biocompatibility Evaluations

"Such a process should generally begin with assessment of the device, including the **material components**, the **manufacturing processes**, the **clinical use of the device**…" Considering this information, the **potential risks from a biocompatibility perspective** should be identified. Considering the potential biological impact, a plan should be developed … **either by biocompatibility testing or other evaluations that appropriately address the risks.**

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Biocompatibility Risk Assessment

Initial thoughts for your change
• Patient contacting material (direct or indirect) • Material Similarities? • Patient contacting surface percentage of change?

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Material Characterization

Manufacturers need to have **solid relationships with suppliers** and ensure full disclosure of materials through:

Manufacturing agreements	Composition disclosures	Processing aide and residual chemical disclosure	Material Safety Data Sheets (MSDS)	Device Master File Information availability to the regulatory authorities

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Percent of Patient Contacting Surface Area

Table 1 — Standard surface areas and extract liquid volumes

Thickness mm	Extraction ratio (surface area or mass/volume) ±10 %	of forms of materials
<0.5		sheet, tubing wall
0.5 to 1.0	3 cm^2/ml	Tubing wall, slab, small molded items
>1.0	3 cm^2/ml	Larger molded items
>1.0	1.25 cm^2/ml	Elastomeric closures
Irregularly shaped solid devices	0.2 g/ml	Powder, pellets, foam, non-absorbent molded items
Irregularly shaped porous devices (low-density materials)	0.1 g/ml	Membranes, textiles

NOTE While there are no standardized methods available at present for testing absorbents and hydrocolloids, a suggested protocol is as follows:

— determine the volume of extraction vehicle that each 0.1 g or 1.0 cm^2 of material absorbs;
— then, in performing the material extraction, add this additional volume to each 0.1 g or 1.0 cm^2 in an extraction mixture.

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Power of Chemical Characterization in Evaluating Changes

Chemical Characterization Definition

IDENTIFICATION OF THE MATERIALS OF CONSTRUCTION, AND THE IDENTIFICATION AND QUANTIFICATION OF THE CHEMICALS PRESENT IN THESE MATERIALS—EITHER INDIVIDUALLY (E.G., AS PART OF A MATERIAL SELECTION PROCESS) OR IN FINISHED MEDICAL DEVICES

- Simple Direct Tests
- **FTIR**
- DSC
- GC-MS
- LC-MS
- ICP-MS
- Physicochemical
- Cytotoxicity

- E&L
  - More complicated (better information)

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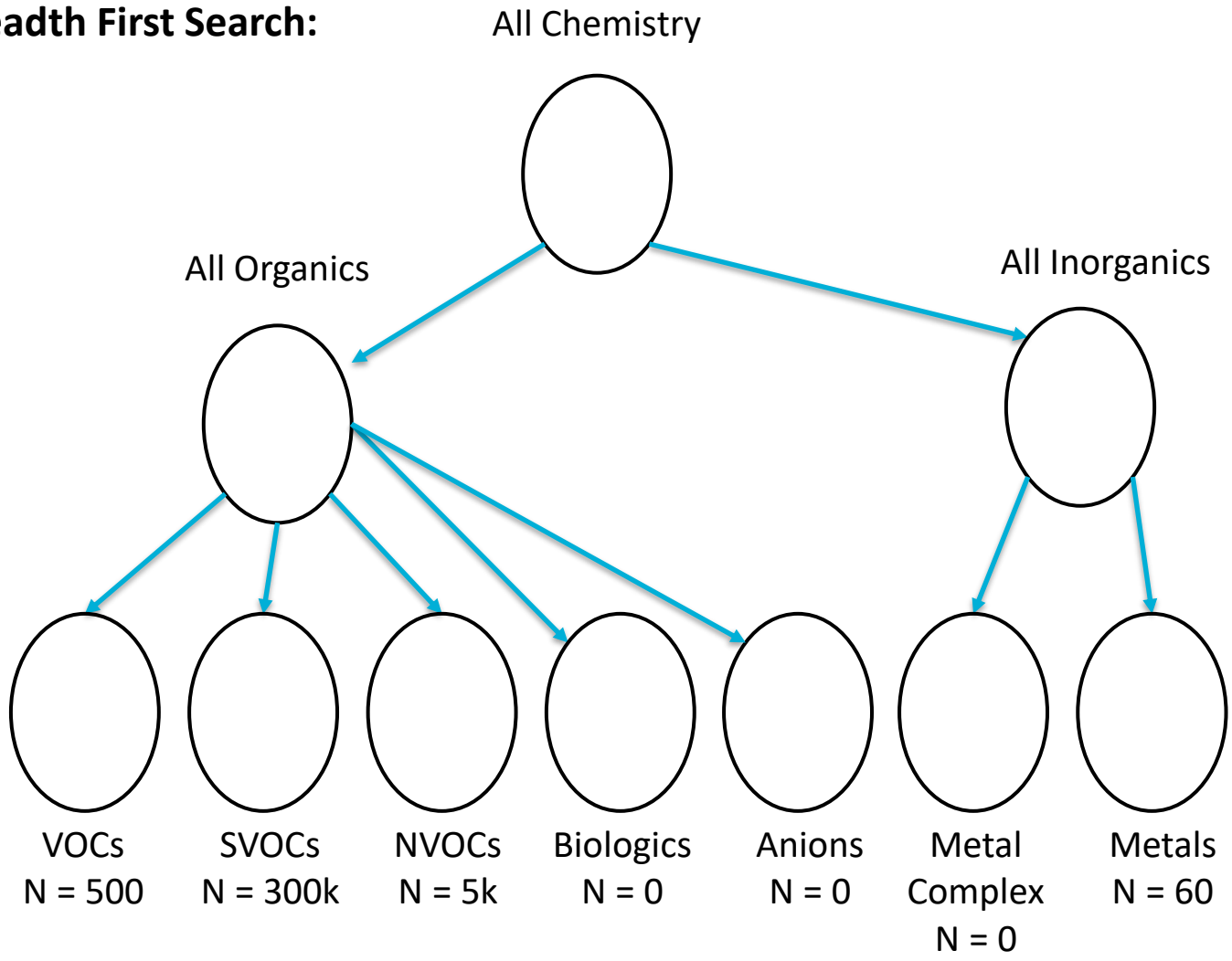
Critical Requirements for Chemistry Part of Chem-Tox

Breadth First Search:



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Critical Requirements for Chemistry Part of Chem-Tox

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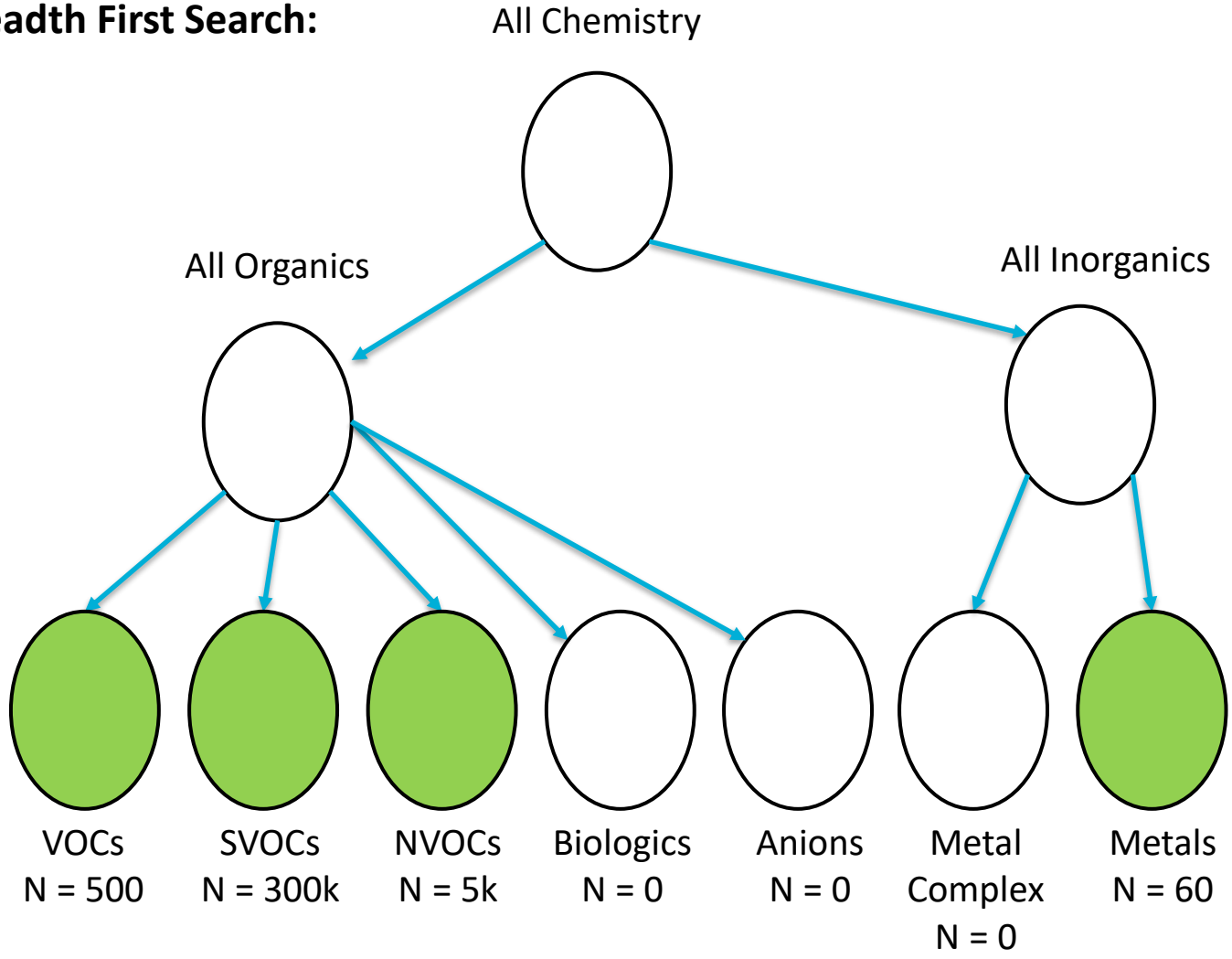

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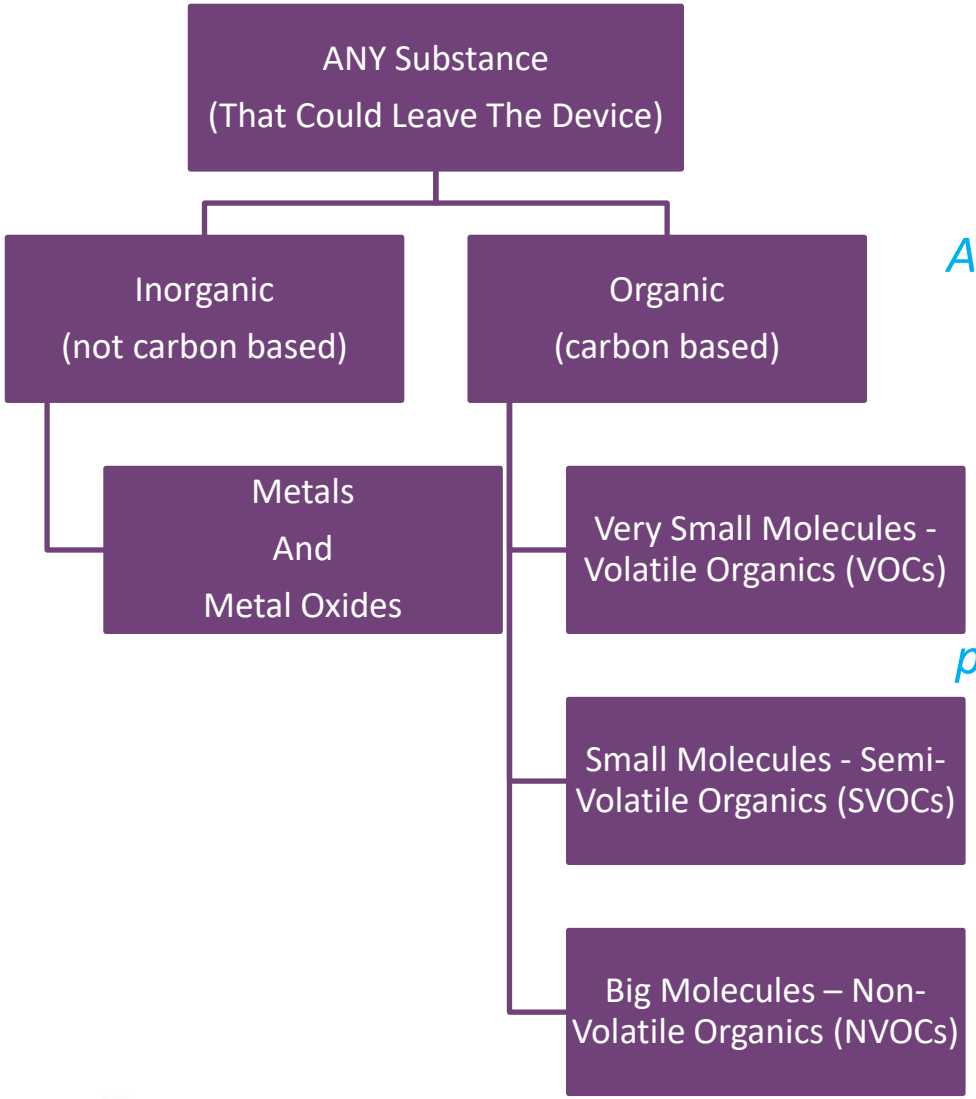
Essential for Toxicology: Capturing as Many Compounds as Possible



Analytically, we cast a **wide net**, looking for essentially everything

From the perspective of *sample preparation*, we also need to **extract as many compounds as possible**

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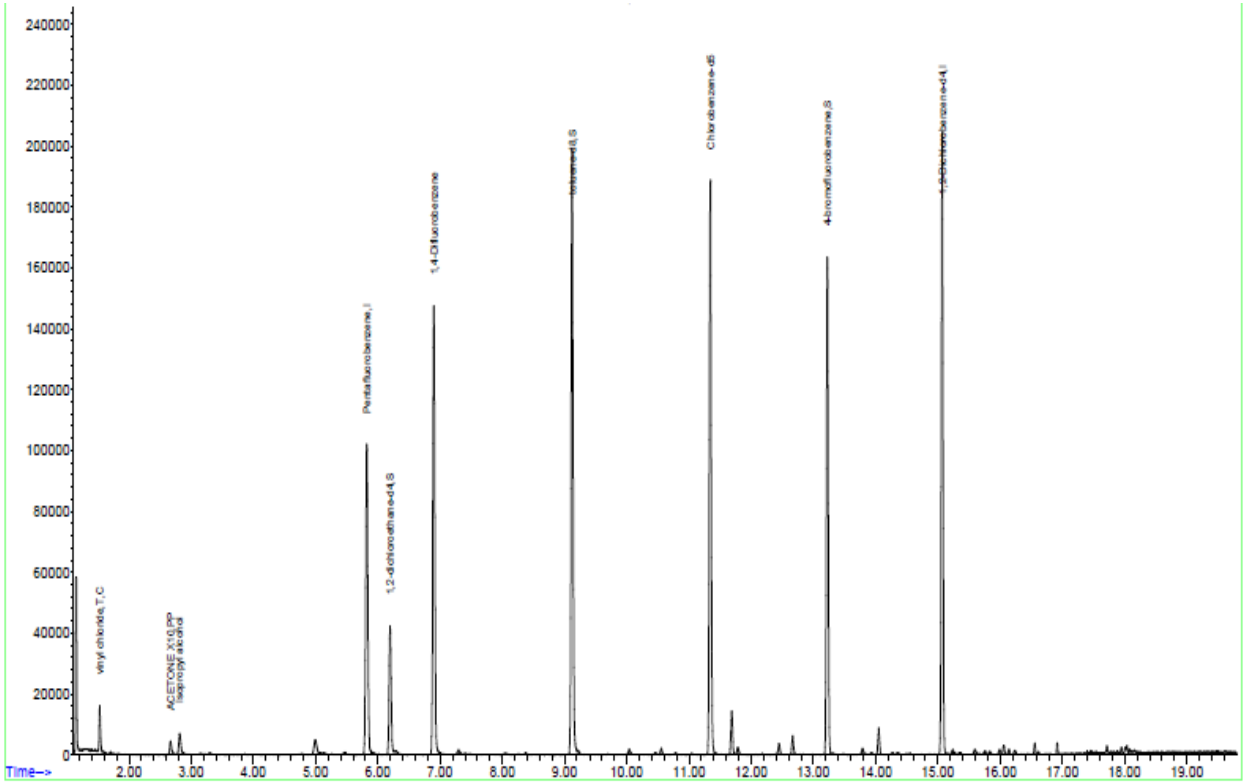
How Does Chromatography Work?

- *Chemical fingerprint from your device*



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Cyto…a Useful Tool

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Cytotoxicity

Sample requirements

- MEM Elution: 120 cm^2 or 4 g
- Agar Overlay: 500 mm^2 or 1g

TAT

- 4 days for preliminary data, 6 days for final report

Usual problems

- Latex, Natural Rubber, Silver, Copper, Dark Inks, Short Curing Times.

Best friend and worst enemy

Plates are made by adding cells in suspension to 6 well cell culture plates.

Sample extracts are added to cells in 6 well culture plates.

Photos by Daniel Olsen at Nelson Labs

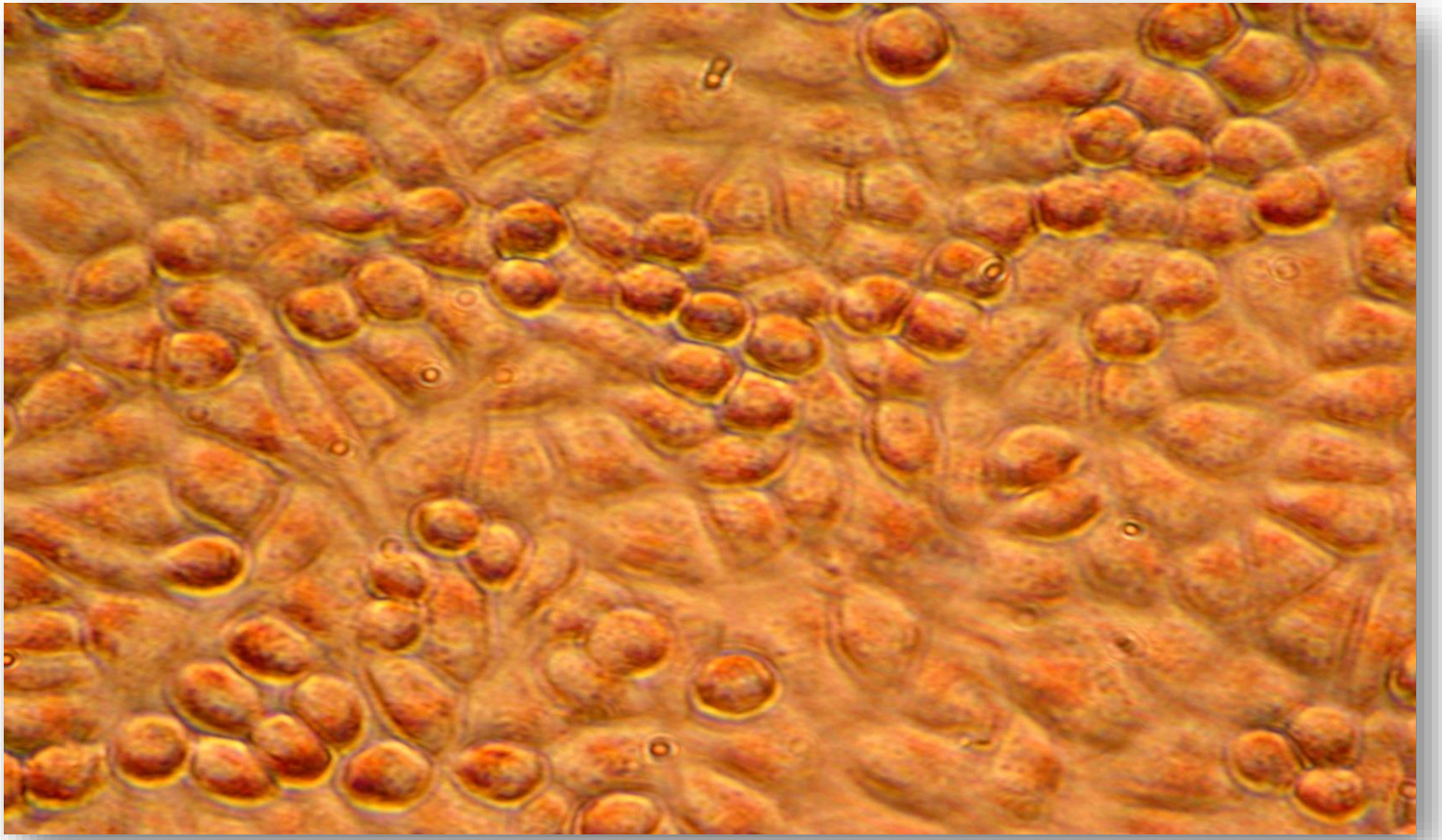
Cytotoxicity

GRADE REACTIVITY DESCRIPTION

0	1	2	3	4
None	Slight	Mild	Moderate	Severe
• Discrete intracytoplasmic granules, no cell lysis.	• Not more than 20% of the cells are rounded, loosely attached, and without intracytoplasmic granules; occasional lysed cells are present.	• Not more than 50% of the cells are rounded and devoid of intra cytoplasmic granules; no extensive cell lysis and empty areas between cells.	• Not more than 70% of the cells are rounded and/or lysed.	• Nearly complete destruction.

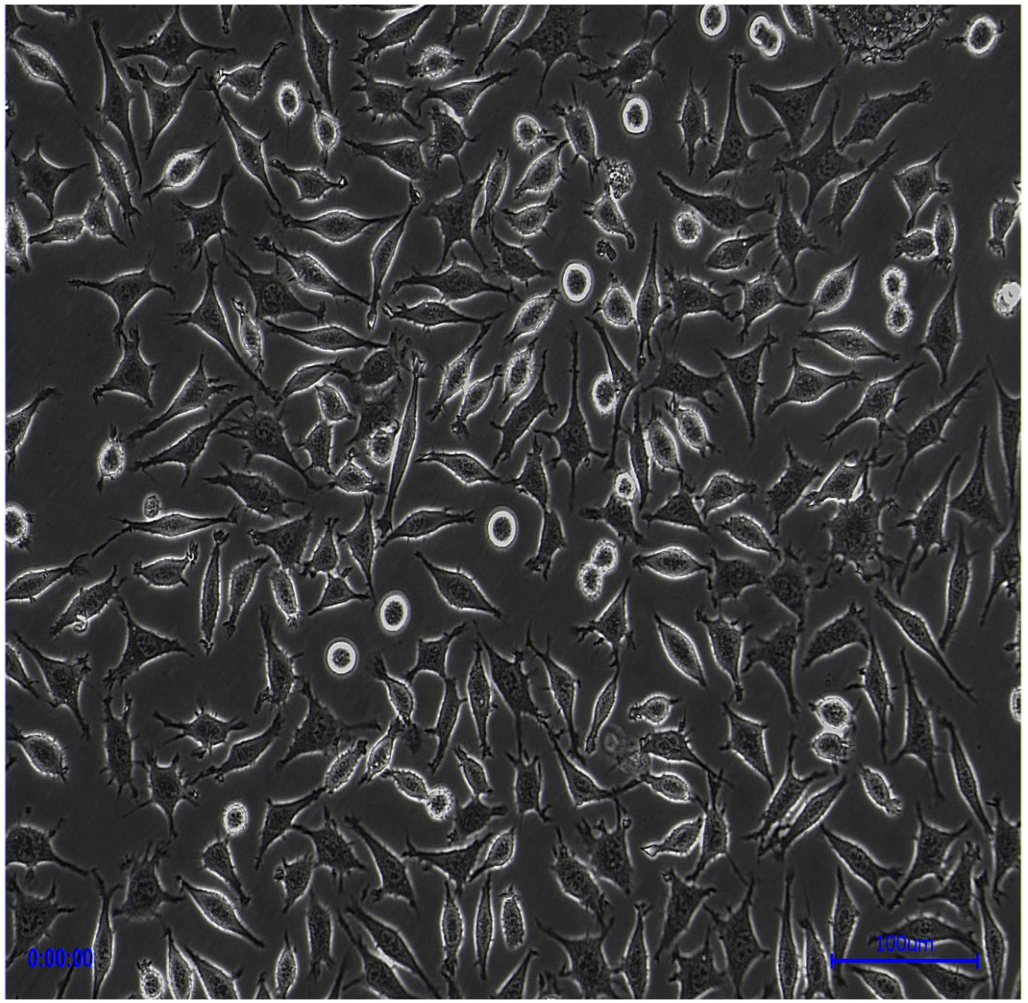
Cytotoxicity Results

Negative Score “0”



Cytotoxicity Results

Positive Score “4”



Courtesy from Arthrex Lab

Making a Report

Biological Evaluation Report

Attachment C: Summary Biocompatibility Documentation

The example table (Table C.1) is provided to illustrate one possible approach to documentation of the biocompatibility information included or referenced in a submission; other approaches are acceptable. Manufacturers are encouraged to use an approach that works for their specific purposes, taking into account the considerations discussed in this guidance document. Note that these are generalized examples to demonstrate documentation and do not necessarily account for every possible consideration.

Table C.1 - Example Table of Summary Biocompatibility Evaluation Information for a Device Submission

Biological endpoint	Location of new test reports provided in submission	Location of test reports leveraged from previous submission	Supporting data from literature	Citation	Test article	Rationale for why additional information isn't needed
Cytotoxicity	Implant: L929 testing (V2, App A-1, pdf p.x/200) Implantation accessory: L929 testing (V3, App B-1, pdf p. x/300)	Implant: [DEVICE NAME] (K# V2, App X-1, pdf p.x/200) Implantation accessory: [DEVICE NAME] (K# V3, App X-1, pdf p.x/300)	n/a	n/a	Identical - see documentation (per Attachment F) V1, pdf p.x/100	Testing conducted on final, sterilized device (implant tested separately from implantation accessory)
Genotoxicity	Implant: chemical characterization (V2, App A-2, pdf p. x/200)	n/a	Test name (e.g., chromosomal aberration): doses with effects and/or doses without effects	Author, Title, Journal, date, volume, and pages	Slight differences between test article and final, sterilized device – see comparison information: V1, pdf p.x/100	Genotoxicity tests are hazard identification tests. Chemical characterization data can be used to confirm that chemicals which elute from the device are not genotoxic per literature.

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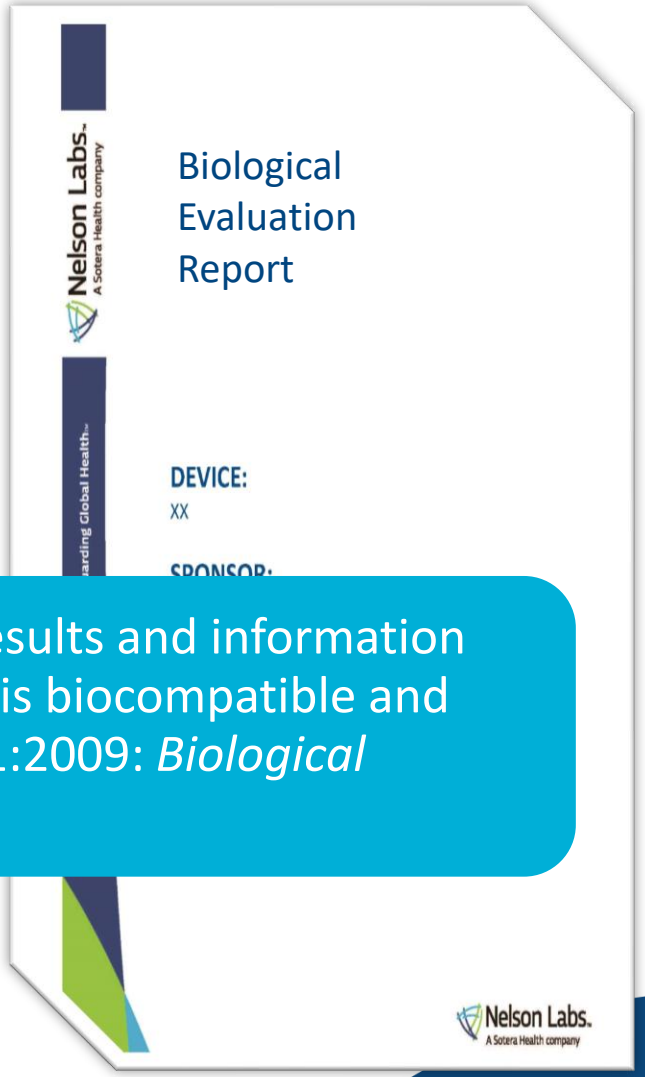
Biological Evaluation Report

CONCLUSION: “Based on the testing results and information summarized in this report, the DEVICE is biocompatible and meets the requirements of ISO10993-1:2009: *Biological evaluation of medical devices – Part 1*.



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QUESTIONS?

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