Chemistry for Toxicological Risk Assessment –Transitions in Expected Approach

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Outline

What is ChemTox?

- One Slide Overview of Fundamentals of Toxicology
- Basic principles of Chemistry for Toxicology

Published Changes to Expectations

- New 10993-18

Unpublished Changes to Expectations

- FDA Feedback on Testing Plans

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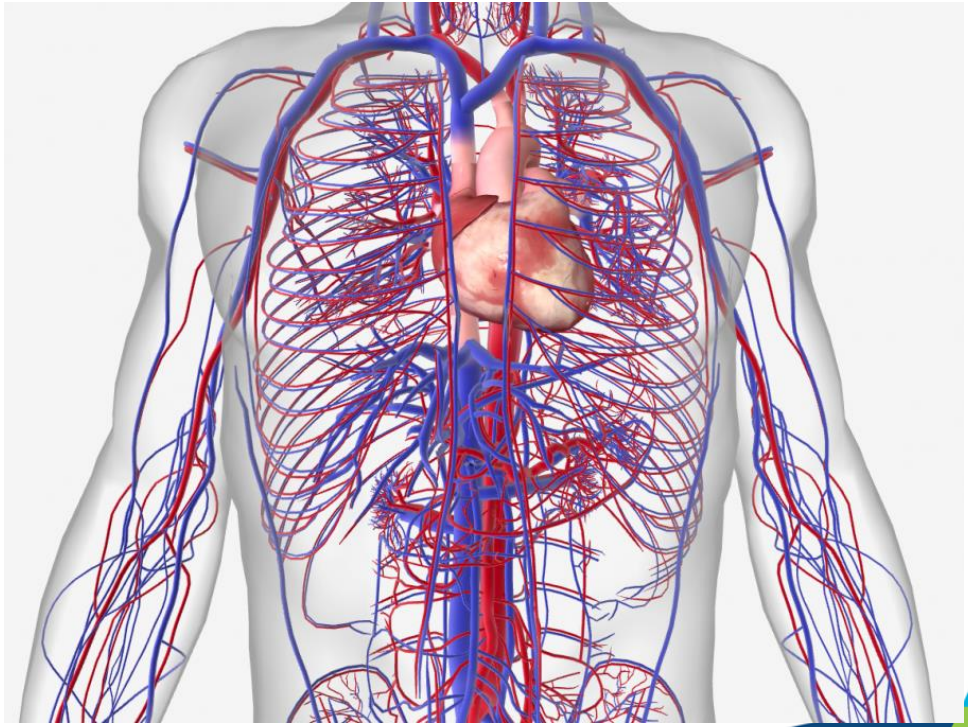
Systemic Toxicological Effects

Endpoints Required for Evaluation:

- Cytotoxicity
- Sensitization
- Irritation
- Material Mediated Pyrogenicity
- Acute Systemic Tox
- Subacute/Subchronic Tox
- Chronic Tox
- Hemocompatibility
- Genotoxicity
- Carcinogenicity
- Implantation



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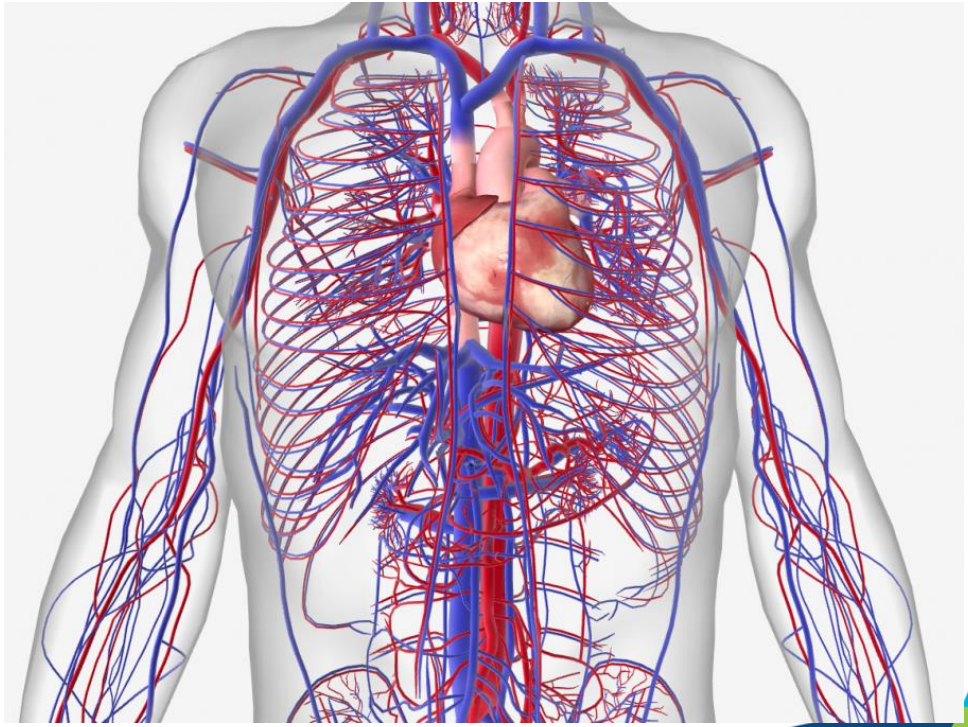
Systemic Toxicological Effects: ChemTox Accepted by FDA

Required Endpoint for Evaluation:

- Cytotoxicity
- Sensitization
- Irritation
- Material Mediated Pyrogenicity
- Acute Systemic Tox ←
- Subacute/Subchronic Tox ←
- Chronic Tox ←
- Hemocompatibility
- Genotoxicity ←
- Carcinogenicity ←
- Implantation



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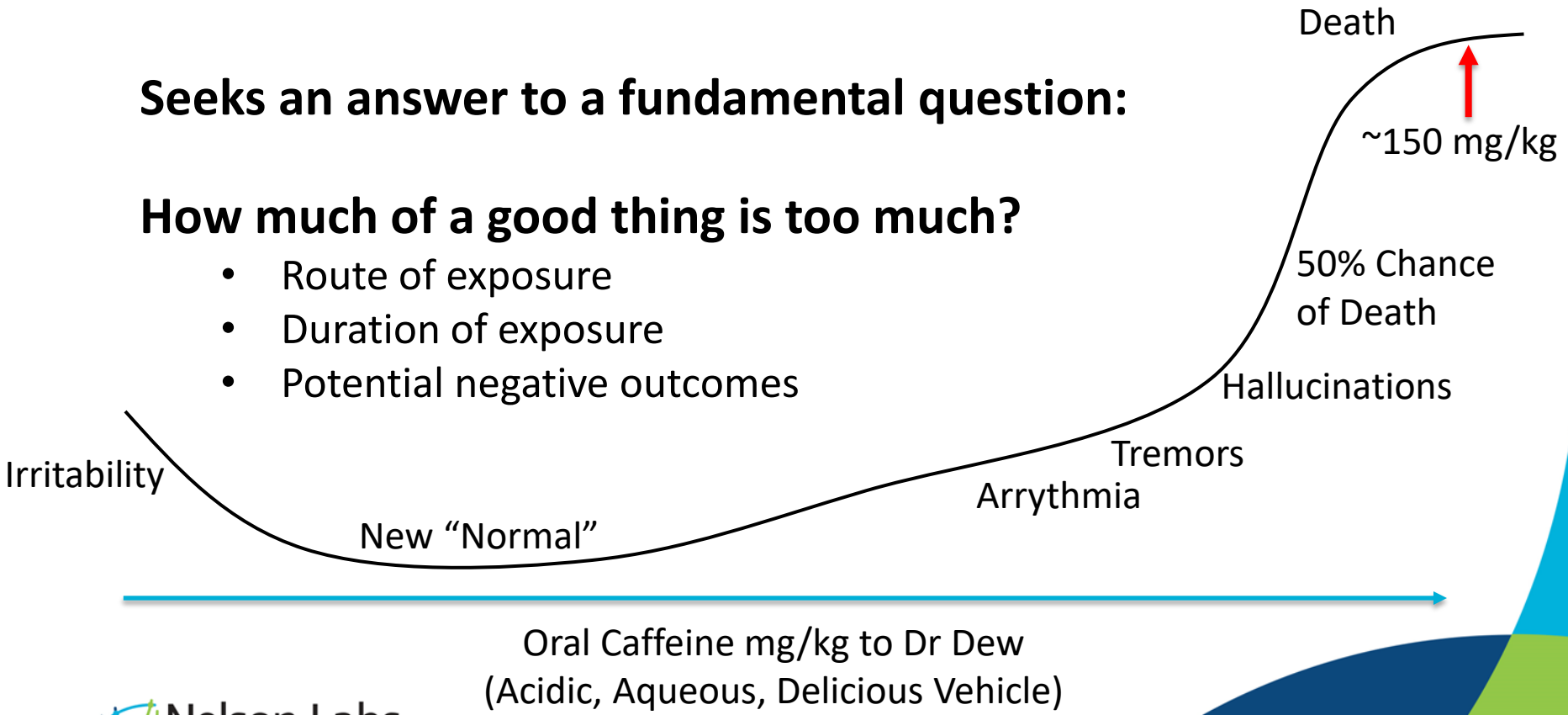
One Slide Intro to Toxicology

11.5 g or 100 Red Bulls

Seeks an answer to a fundamental question:

How much of a good thing is too much?

- Route of exposure
- Duration of exposure
- Potential negative outcomes



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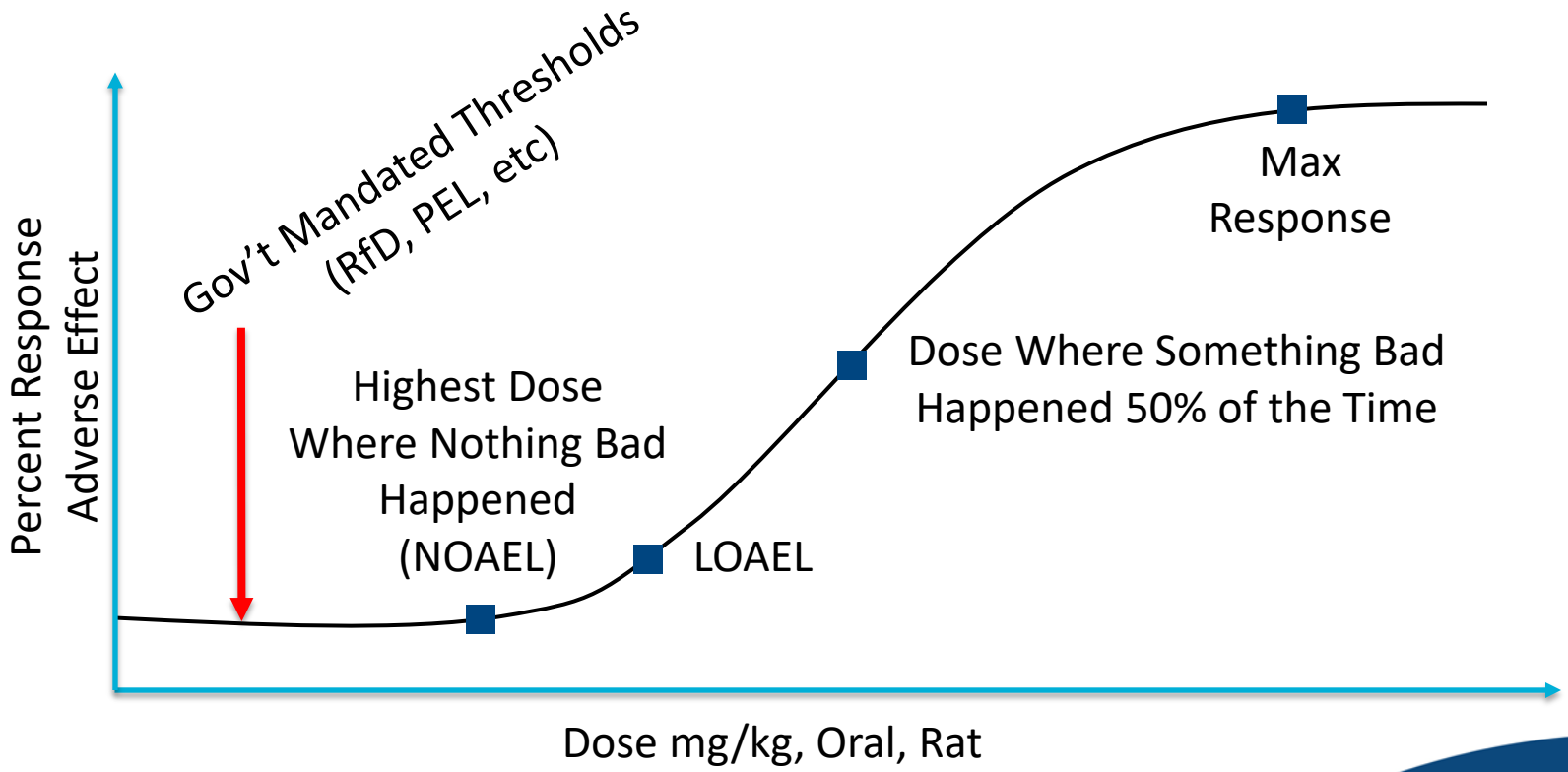
Dose/Response Curves: Xenobiotics



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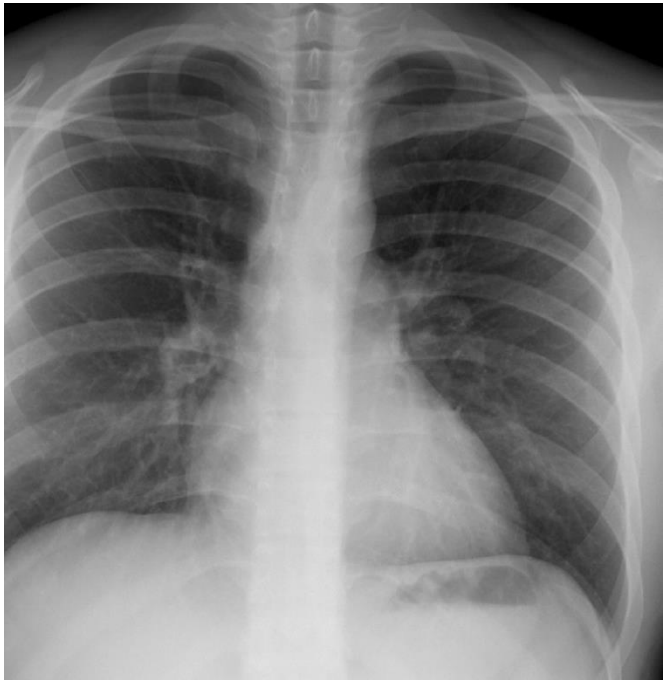
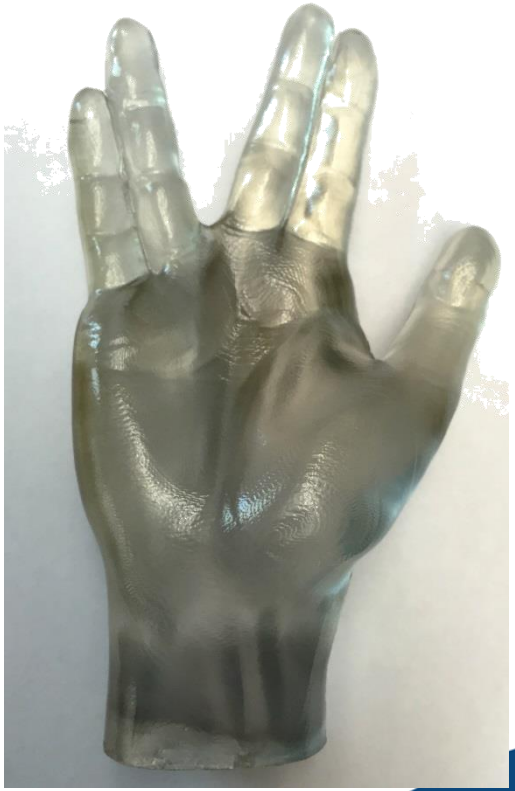
Chemistry Strategy Framed by Problem





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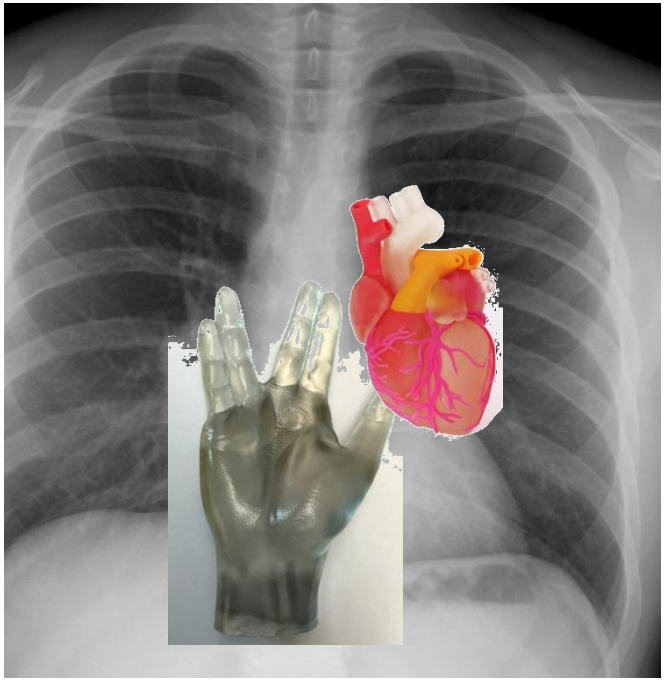
Chemistry Strategy Framed by Problem



- **ANY** substance that could realistically leave the device during use and enter the body
  - Metals
  - Production oils and other residuals
  - Plastic additives
  - Byproducts
- **Ignore substances that are impossible/improbable**

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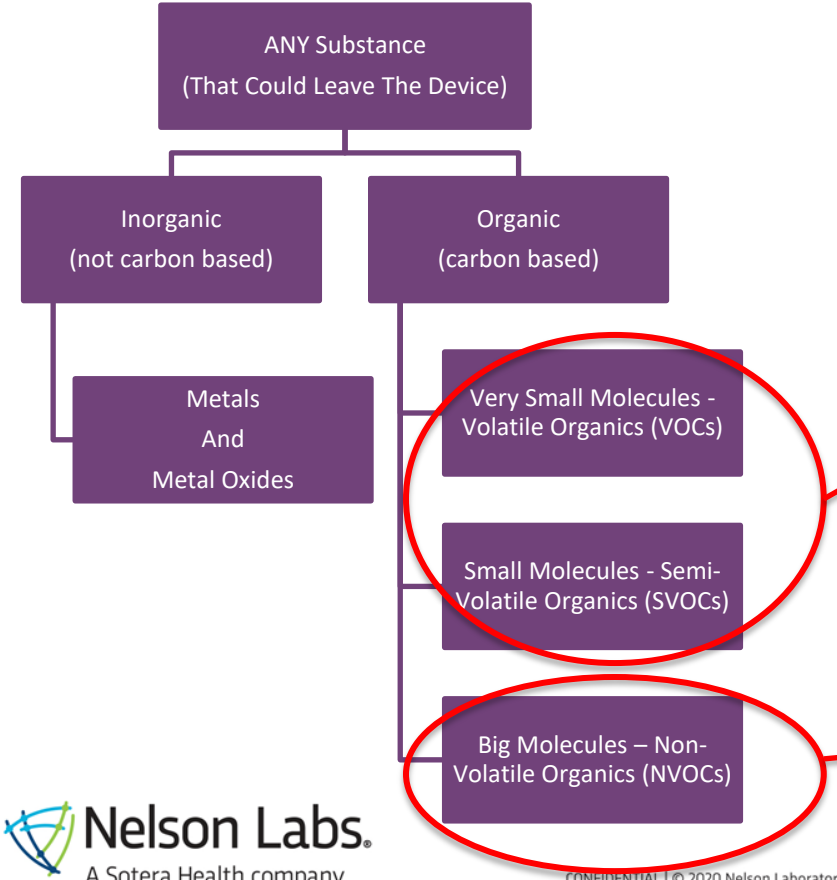
Suite of Analytical Methods



Small molecules
evaporate easily,
great for
gas chromatography
(**GC**)

Big molecules
do not evaporate easily,
great for
liquid chromatography
(**LC**)

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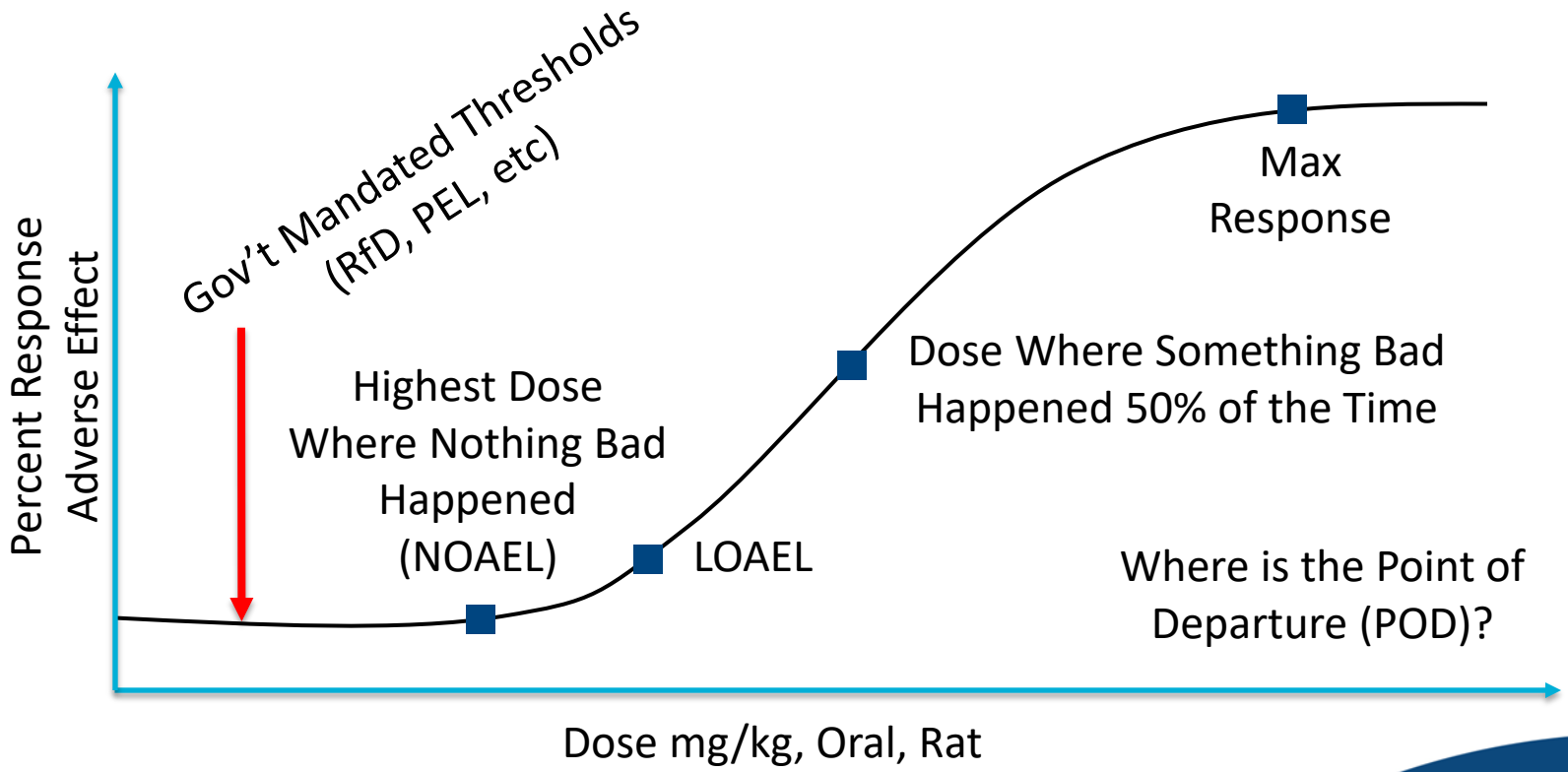
Critical Criteria for Chemistry: Sufficient Breadth and Sensitivity



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Updated 10993-18 Published

- ISO 10993-18 (2005): 17 pages
- ISO 10993-18 (2020): 79 pages

Major revision of the whole concept of chemical characterisation:

- Broader definition of chemical characterisation
- Introduction of the concept of Analytical Evaluation Threshold (AET)
- Definition of extractable testing
- Definition of leachable testing
- Clarification on the extraction procedures and analytical techniques to be used during chemical testing

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Updated 10993-18 Published

3.2
analytical evaluation threshold
AET
threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment (see Annex E)

3.3
analytically expedient
situation where an extraction vehicle can be directly evaluated with generally available analytical methods with the sensitivity and selectivity necessary to achieve a designated reporting threshold such as the AET

3.16
extractables
substances that are released from a medical device or material of construction when the medical device or material is extracted using laboratory extraction conditions and vehicles

3.22
leachable
substance that is released from a medical device or material during its clinical use

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Extraction Duration

Table 2. Recommended Extraction Conditions

Contact Category	Recommended Extraction Conditions	Credible Alternatives
Limited contact devices	Simulated use conditions[a]	Exaggerated conditions
Prolonged contact devices	Exhaustive conditions	Exaggerated conditions[b,c]
Long-term contact devices	Exhaustive conditions	Exaggerated conditions[b,c,d]

[a] With suitable justification.

Source: ISO 10993-18 (2020)

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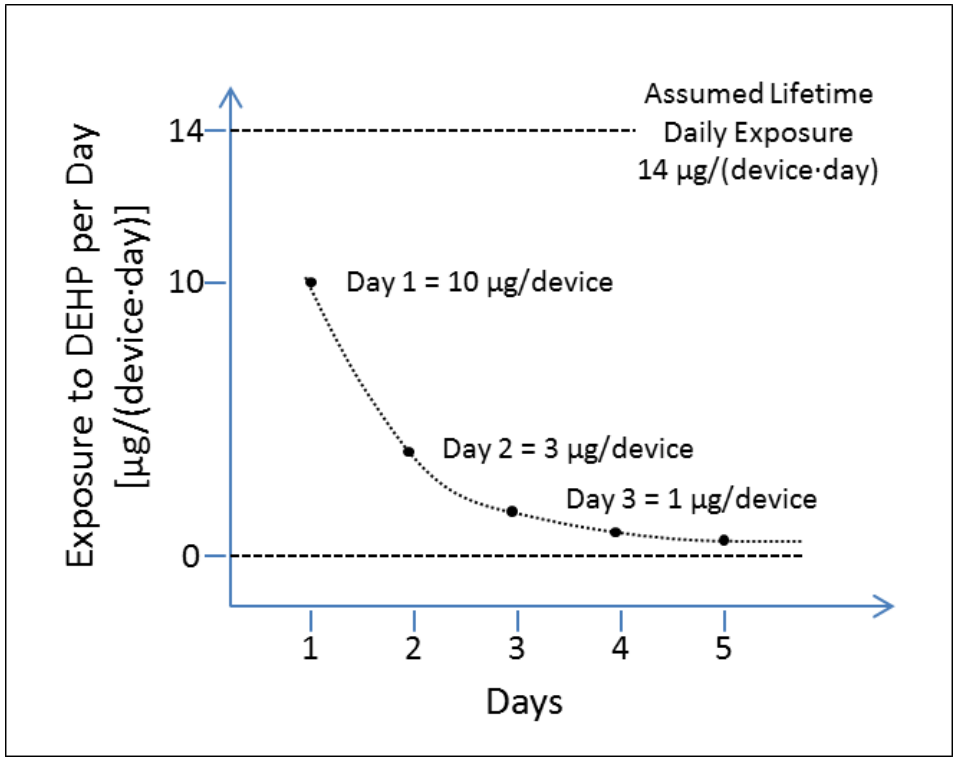
SIDEBAR: Exhaustive Extractions for Med Devices



- Common practice for our toxicologists is to assume that the total amount of compound extracted over 72 hours at 50 °C is the chronic lifetime daily exposure
- If the material doesn't degrade, then *physics demands that the rate of release decays*
- In the example to the left, for a PVC device, the actual total lifetime exposure is estimated to be 16 µg (integral of area under the curve)
- **The assumed lifetime exposure is 350,000 µg (14 µg/day × 25,000 days)**

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Determining the Required Analytical Sensitivity

- Goal is to minimize risk related to undetected compounds below the analytical sensitivity
- Consideration must be given to uncertainty in accuracy of measurement (generally a factor of 2 to 4)

Table 1 — Recommended ICH M7(R1) (2017) TTC values based on ISO 10993-1 medical device contact category

Medical device contact category	Limited (<24 h)	Prolonged (24 h to 30 d)	Long-term[a] (>30 d)		
Duration of body contact	≤ 1 month		> 1 month to 12 months	> 1 year to 10 years	> 10 years to lifetime
Daily intake (µg/d) of any one constituent	120		20	10	1,5[b]

[a] Long-term includes devices commonly described as permanent contacting (see ISO 10993-1).

[b] The 1,5 µg/d value is based on 10^{-5} cancer risk and 60 kg (adult) body weight[6][17].

PD ISO/TS 21726:2019

TECHNICAL SPECIFICATION

ISO/TS 21726

First edition
2019-02-25

luation of medical
plication of the threshold
al concern (TTC) for
compatibility of medical
uents

Évaluation biologique des dispositifs médicaux — Application du seuil de préoccupation toxicologique (TTC) pour évaluer la biocompatibilité des substances extractibles des dispositifs médicaux

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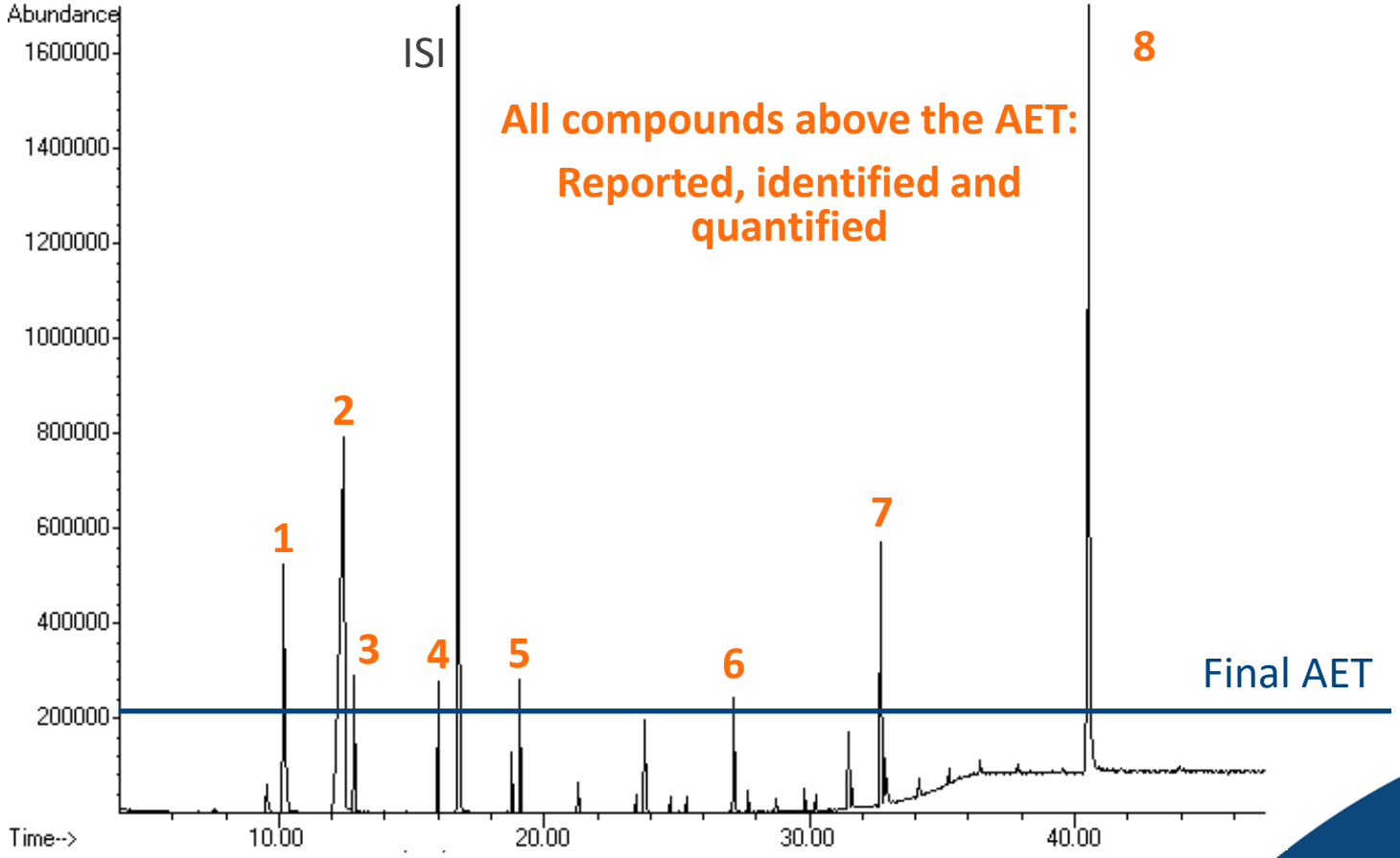
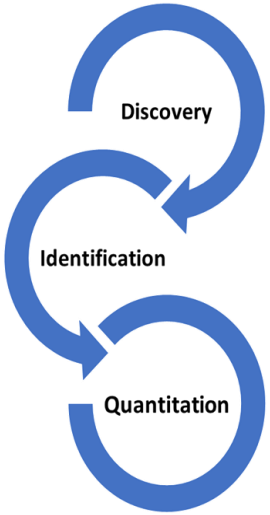
The Analytical Evaluation Threshold



Expected Analytical Techniques



Screening

1. Are there substances unique to the sample (versus an appropriate blank) that are present in the sample above a certain concentration threshold?
2. If yes, what are they identities of those substances?
3. If yes, what are the concent
of those substances?

Targ g

Qu
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s the
ntration of the
specified substance?

NET-FISH

FLY-FISHING

Screening: mentioned 46 times in the ISO 10993-18 (2020)

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Feedback from FDA on Testing Plans

Regarding Extraction Solvents:

- *We recommend that for implants with permanent contact (> 30 days),* ***exhaustive extraction*** *should be conducted with polar, mid polar, and non-polar solvents to generate worst-case extractables profiles. Therefore, we recommend that you conduct exhaustive extraction with final finished implantable devices using appropriate solvents (e.g.,* ***water, isopropyl alcohol, and hexane****)*
- *Your test protocols indicated that your testing was limited to isopropyl alcohol (IPA) as the non-polar solvent. However,* ***based on the polarity index, IPA is considered as a medium polar extraction solvent*** *(polarity index=3.9).*

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Feedback from FDA on Testing Plans

Regarding Analytical Methods:

- *FDA typically recommends that all extracts are analyzed using **ESI** in addition to any **APCI** analysis that is performed.*
- *We recommend that method qualification includes **multiple standards** at a range of retention times so that the reporting limit and dynamic range is demonstrated for analytes with a variety of chemical properties. For GC/MS, we recommend **a minimum of three reference standards** are used.*
- *We recommend that the **approach to sample concentration is justified** by demonstrating the methodology does not results in analyte loss using control compounds of a range of volatilities and concentrations.*

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Feedback from FDA on Testing Plans

Regarding Identifications:

- *We **do not** recommend **choosing a structure associated with the highest match factor** without providing a justification for eliminating other potential matches.*
- ***All potential identifications should be provided** so that they can be considered in the toxicological risk assessment.*
- *Substances for which only partial structure data is available should be **designated as unknown** in the test report and for toxicological risk assessment.*
- *If a class of substances is to be listed as the identification, then **all potential members of the class should be provided**.*

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Feedback from FDA on Testing Plans

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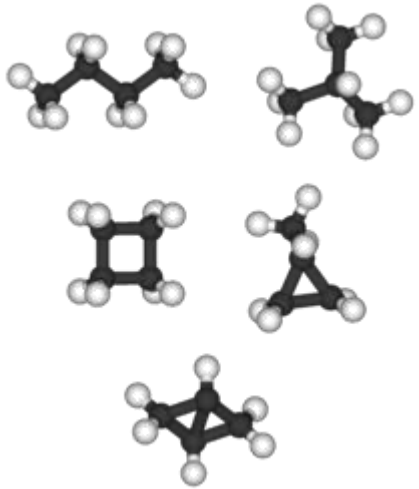

C4 Alkanes: 2 members
C5 Alkanes: 3 members
C6 Alkanes: 5 members
C12 Alkanes: 355 members
C32 Alkanes: 27.7 billion members

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Feedback from FDA on Testing Plans

Regarding Reporting, the Following Should be Included:

- ***Calibration data*** *that demonstrates that suitability of the calibration method across the range needed for quantification.*
- ***Chromatographic data*** *that includes labeling to discern retention time and relative signal intensity.*
- ***Substance information*** *when higher than the AET:*
  - *(1) Retention time, (2) proposed identity(ies), (3) chemical name (e.g. IUPAC name), (4) CAS number, (5) structural descriptor (e.g. SMILEs), (6) identification confidence level, (7) type of identification data (e.g. spectra library match), (8) quantification method (e.g. fully quantitative using an authentic standard, semi-quantitative based on a relative response factor, or semi-quantitative using a surrogate response factor), (9) concentration (e.g. in µg/ml), and (10) quantity (µg/device).*

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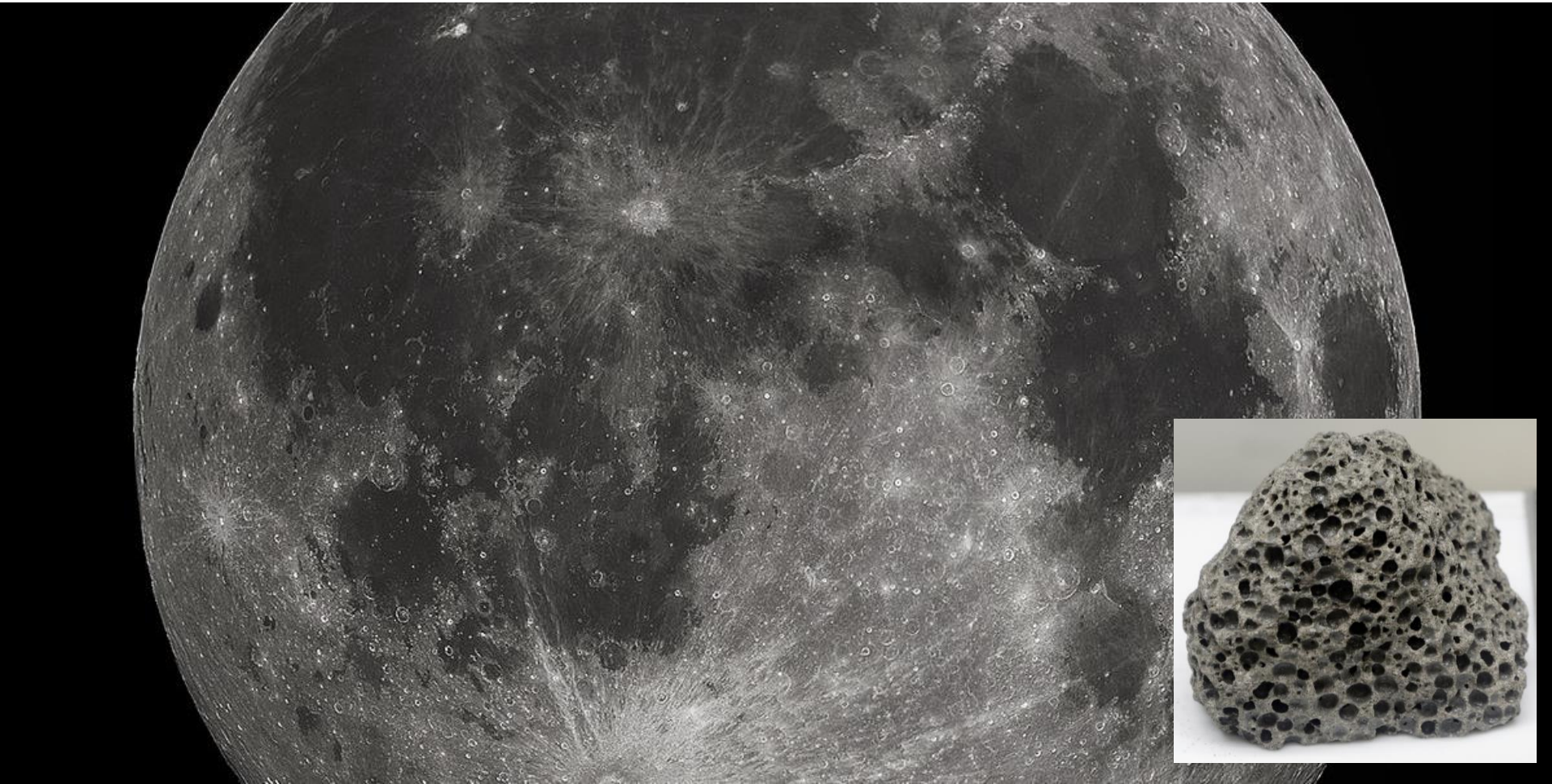
What the FDA Wants



Conclusion on Toxicological Assessments

- Biocompatibility evaluations must be strategic & science based
- ***Material Characterization***: Thorough understanding of the device materials and processing can help to minimize biocompatibility testing
- ***Chemical Characterization***: Provides the key information needed to conduct a proper risk toxicological assessment
- Goals: Save animal life, save time, save money, and **IMPROVE PATIENT CARE**!

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Questions?

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