Mastering Biocompatibility Testing in a Shifting Landscape

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Mastering Biocompatibility Testing in a Shifting Landscape: Setting the Stage – Industry Perspective

Danese Joiner-Fox
Senior Manager Regulatory Affairs
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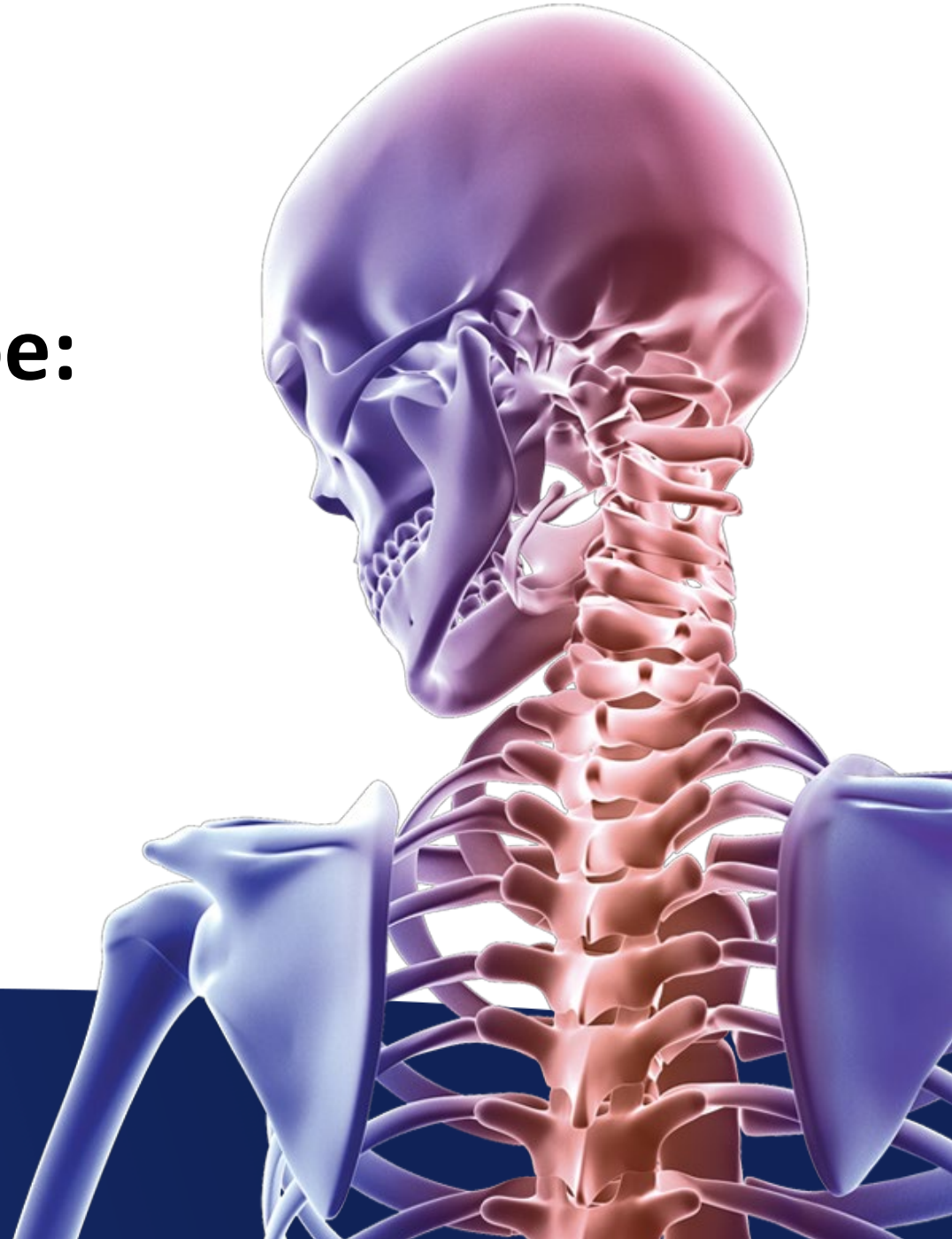

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Conducting Biocompatibility Assessments Can be Challenging

Time

Money

Sample (Devices)

Additional Challenges

- Addressing all recommended endpoints in the FDA biocompatibility guidance document
- Addressing the biocompatibility of instruments
  - Sometimes the focus is on implants
- Inability to compare representative samples that are used for physical testing to the final finished device

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	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	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (> 30 d)													
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	X	O	X		X					
		C	X	X	X	X	O	X	X	X		X			
	Breached or compromised surface	A	X	X	X	X	X								
		B	X	X	X	X	X	X		X					
		C	X	X	X	X	X	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X	X				X				
		B	X	X	X	X	X	X			X				
		C	X	X	X	X	X	X	X	X	X	X	X		
	Tissue+/bone/ dentin	A	X	X	X	X	X								
		B	X	X	X	X	X	X	X	X					
		C	X	X	X	X	X	X	X	X		X	X		
	Circulating blood	A	X	X	X	X	X		X		X				
		B	X	X	X	X	X	X	X	X	X				

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

Additional Challenges

- Assessments that focus only on the biocompatibility of the material and fail to consider the effects of manufacturing, geometry, and sterilization
- Not having the submission numbers of utilized previously cleared or approved devices
- Not having full test reports
- Strategies to use Chemical characterization to address all biocompatibility endpoints
- Not accepted for sensitization, irritation and material mediated pyrogenicity

Best Practices

- Balance providing the necessary information for review
  - Providing extraneous or unnecessary information may confuse a reviewer and potentially cause delays
- Address all recommended biocompatibility endpoints per the FDA guidance document
- Provide complete test reports
  - Fully describe testing conditions, deviations, results, and conclusions

Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions

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Guidance for Industry and Food and Drug Administration Staff

Best Practices

- When differences between the new device and the existing device (e.g., manufacturing or sterilization) are not expected to adversely impact recommended endpoints, valid scientific evidence or justifications can be a successful approach

	Sterilization Method	Manufacturing
Subject Device	Method A	Method A
Predicate Device	Method B	Method B
Why difference does not impact any biocomp. endpoints	Justification addressing all endpoints	

- With chem. char., carefully consider the right extraction vehicles, worst case patient exposure scenarios for extraction, the appropriate analytical methods, limits of detection, and the risk of each biocompatibility endpoint for all detected elements

Best Practices

- Summaries in addition to full test reports can be helpful tools to highlight key information

Biocompatibility Endpoint	Result	Attachment
Cytotoxicity	Subject device passed	Attachment C
Irritation	Subject device a non-irritant	Attachment D
Sensitization	Subject device a non-sensitizer	Attachment E

- Be clear and comprehensive in the biocompatibility assessment
- **Including a passivation step to metals can reduce the need for biocompatibility testing**

Thank You

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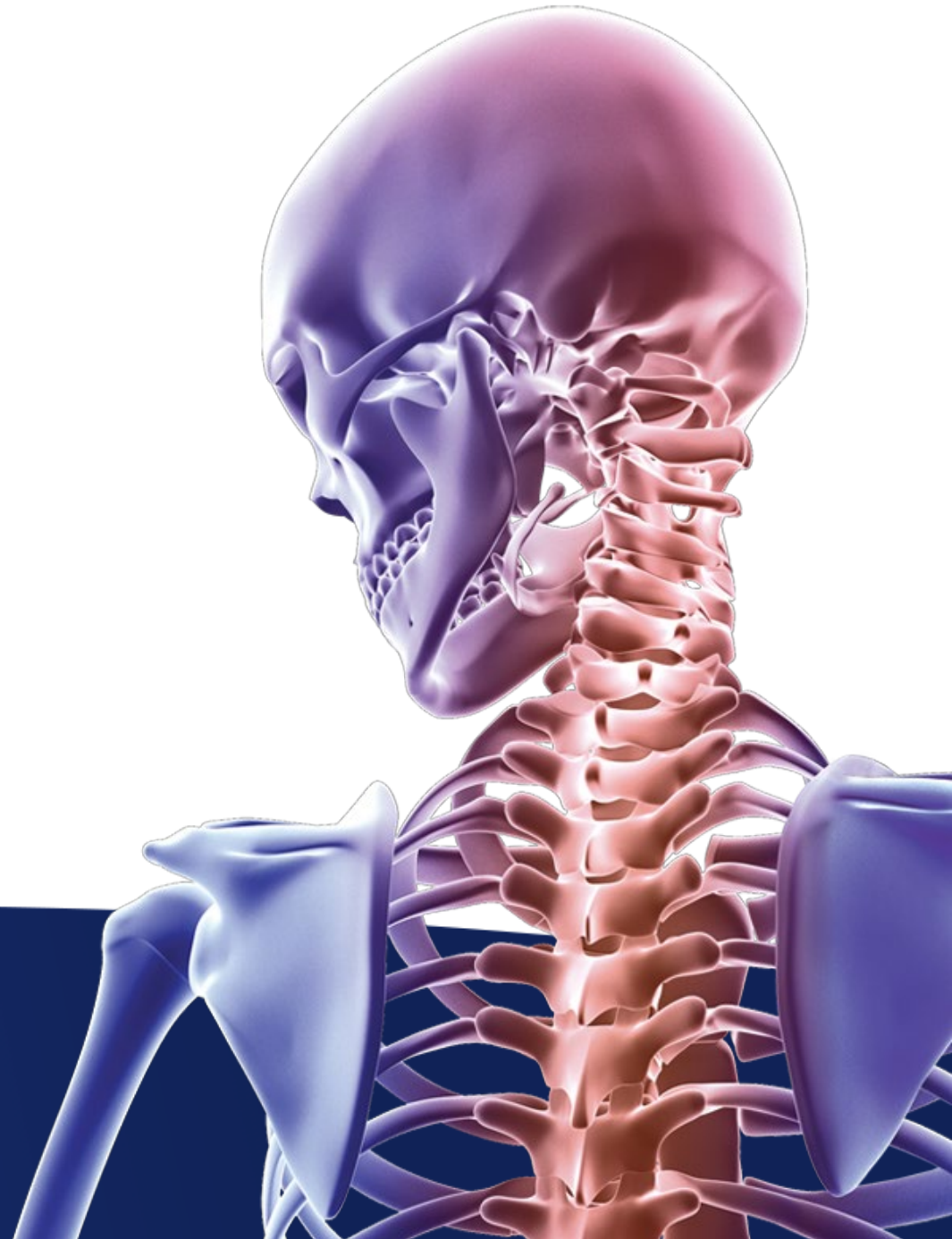

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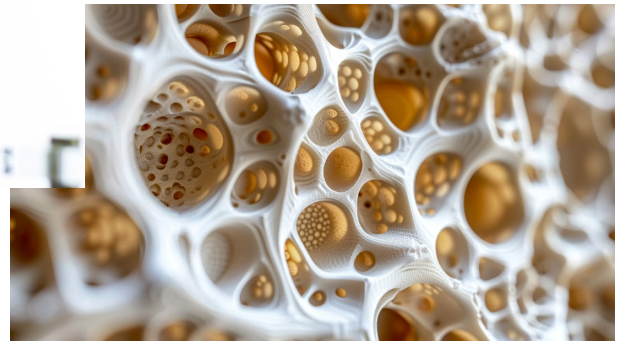
Biocompatibility: Planning and Testing

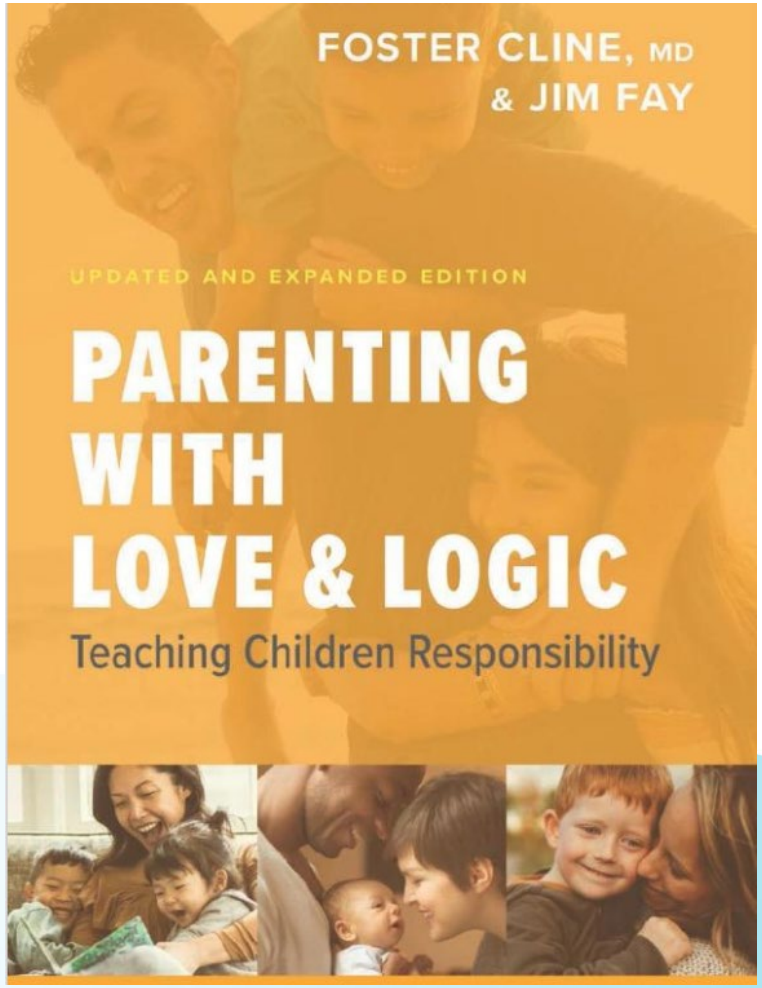
HELIN RÄÄGEL, PHD
PRINCIPAL BIOCOMPATIBILITY EXPERT

Titanium Implant
Anodized, Passivated

Complex Implant
3D Printed, Coated, Multiple Materials



Both are bone implants – but do they carry the same risk?



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Where to Start?

- Intended use
- Materials and processing info
- Relevant available information:
    - Well-known and wetted materials and processing (per ASTM)
    - Previous testing data on equivalent device (manufactured by you)
    - Clinical or real-world data
- Define gaps in available data vs potential risks
- Define a testing plan (if needed to fill gaps)

Biological Evaluation Plan

Share the PLAN with your regulatory reviewer

> Sponsors are advised to initiate discussions with the appropriate Center and review division prior to the initiation of long-term testing of any new device to ensure that, if testing is needed, the proper testing will be conducted.

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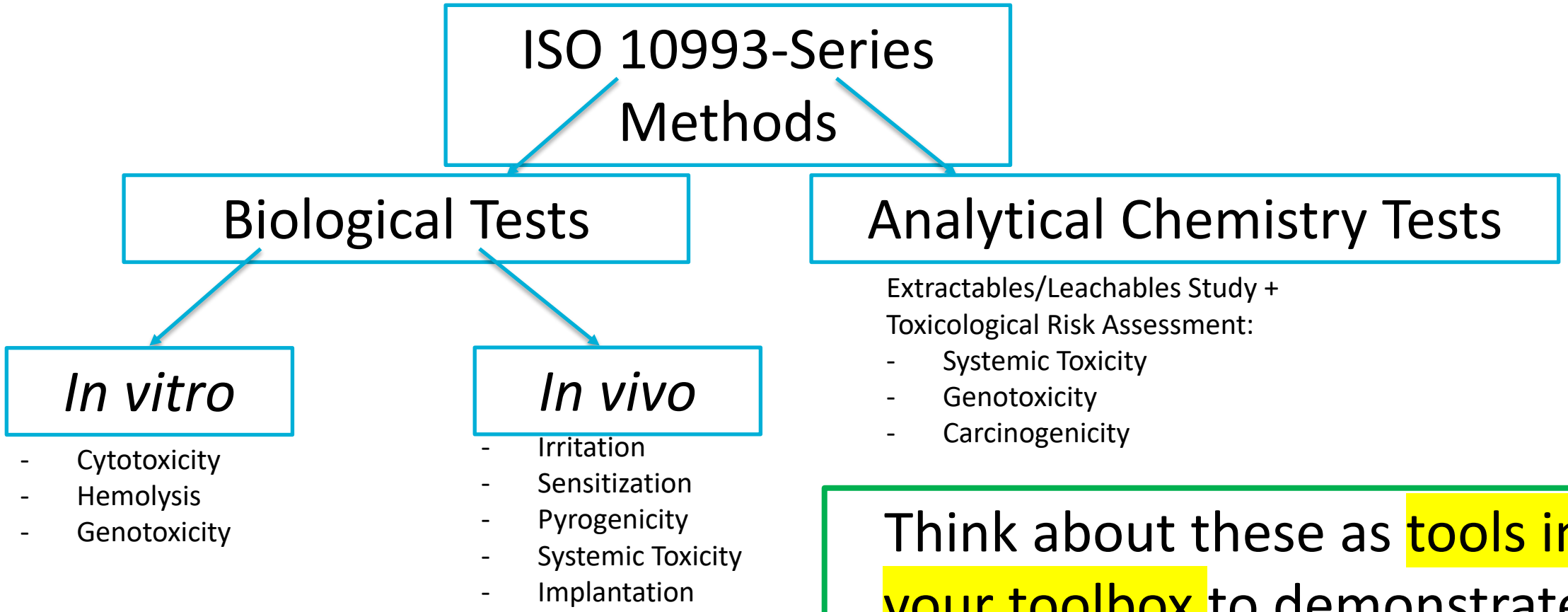
What Test Methods are Available for Use?



Think about these as tools in your toolbox to demonstrate that your device has low reactivity!

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- **Expect scrutiny**
- What can you do?
  - Characterize particulates
  - Investigate potential source
  - Consistent within batches?
  - Assess clinical risk
  - Document findings and conclusion

Call Helin

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Engineering the extraordinary

Taring the Scales: Biocompatibility Evaluations Within a Weight-of-Evidence Framework

June 11th, 2024
Steph Street, PhD

Legal Disclaimer

The presenter has no conflicts of interest.

This presentation reflects the opinions of the presenter and not those of Medtronic plc.

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Weight-of-Evidence Framework

Quantitative Scoring System

- WoE framework publication.
  - Street, S. M., & Christian, W. V. (2024). Taring the scales: Weight-of-Evidence framework for biocompatibility evaluations. *Regulatory Toxicology and Pharmacology*, 105590.
- Framework developed to score data inputs and determine strength of the biocompatibility profile based on the quality and robustness of the data.

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How Is Biocompatibility Data Evaluated?

Standard Guidance

- ISO 10993-1:2018:
  - “ISO 10993 series is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and **judge the outcome of the evaluation** for each medical device, **taking into consideration all the factors relevant to the medical device**, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.”

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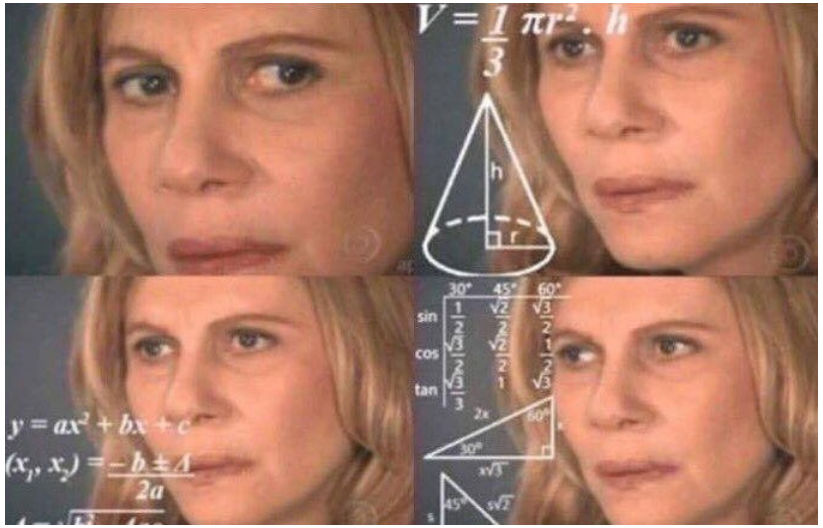

https://knowyourmeme.com/memes/math-lady-confused-lady

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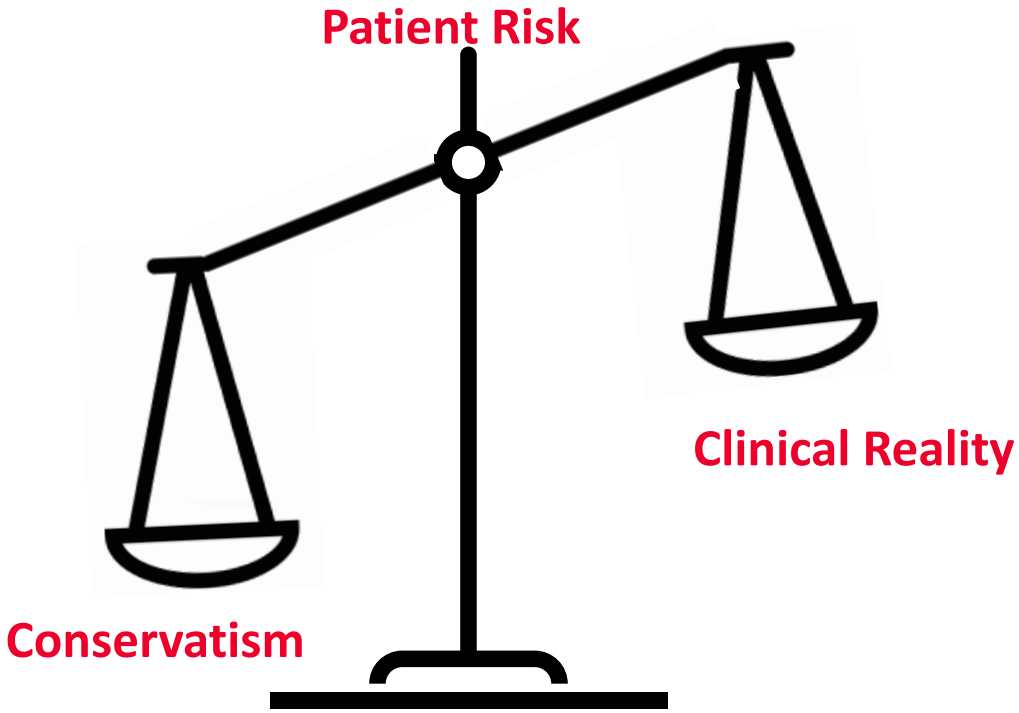
How is Biocompatibility Data Evaluated?

Current Practice

- Data is often evaluated individually.
- Assays typically include several conservative assumptions and exaggerated exposure scenarios.
  - These layers of conservatism can result in an over-estimation of risk.



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How Is Biocompatibility Data Evaluated?

Effects of Exaggeration

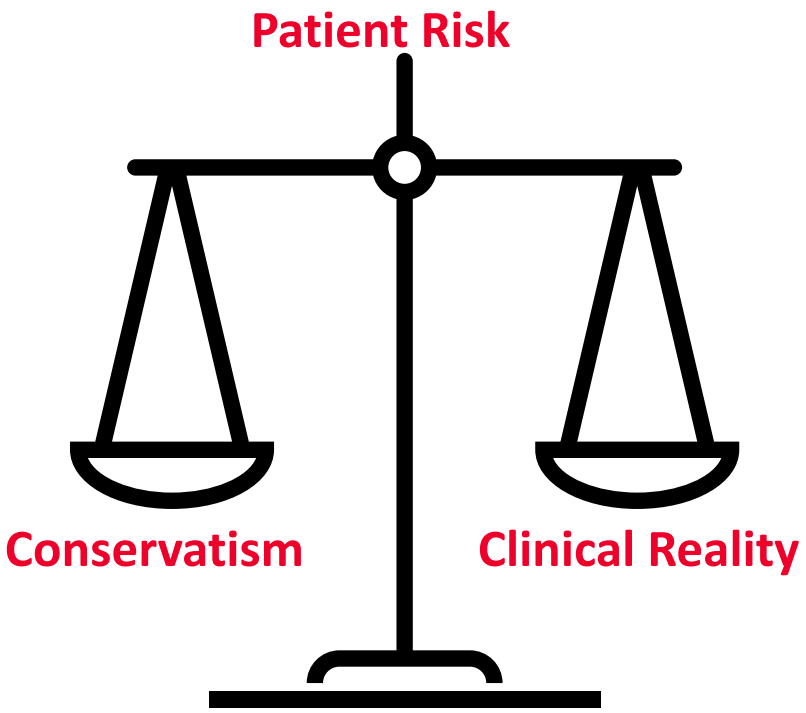
Data Type	Exaggeration Point	Potential Result	Potential Effect
Chemical characterization	DBT and AET (reporting limit)	Lower DBT leads to lower AET	Increased number of E&Ls
	Extraction solvents	Harsh, non-physiologically relevant	Increased number and mass of E&Ls
Toxicological risk assessment	Uncertainty factors	Conservative application decreases tolerable intake	Unfavorable or low MOS values
Biological endpoint testing	*In vitro* assay	Absence of toxicokinetics, unclear relationship/extrapolation to *in vivo* results	False positive results
	ISO 10993-12 recommended extraction conditions	Dose to assay larger than clinical exposure	

DBT – Dose Based Threshold; AET – Analytical Evaluation Threshold; E&L – Extractables and Leachables

How is Biocompatibility Data Evaluated?

Proposed Future State

- Weight-of-Evidence (WoE) approach.
  - This will allow us to assess the totality of the biological evaluation inputs and contextualize the data to improve our ability to arrive at accurate decisions regarding risk.



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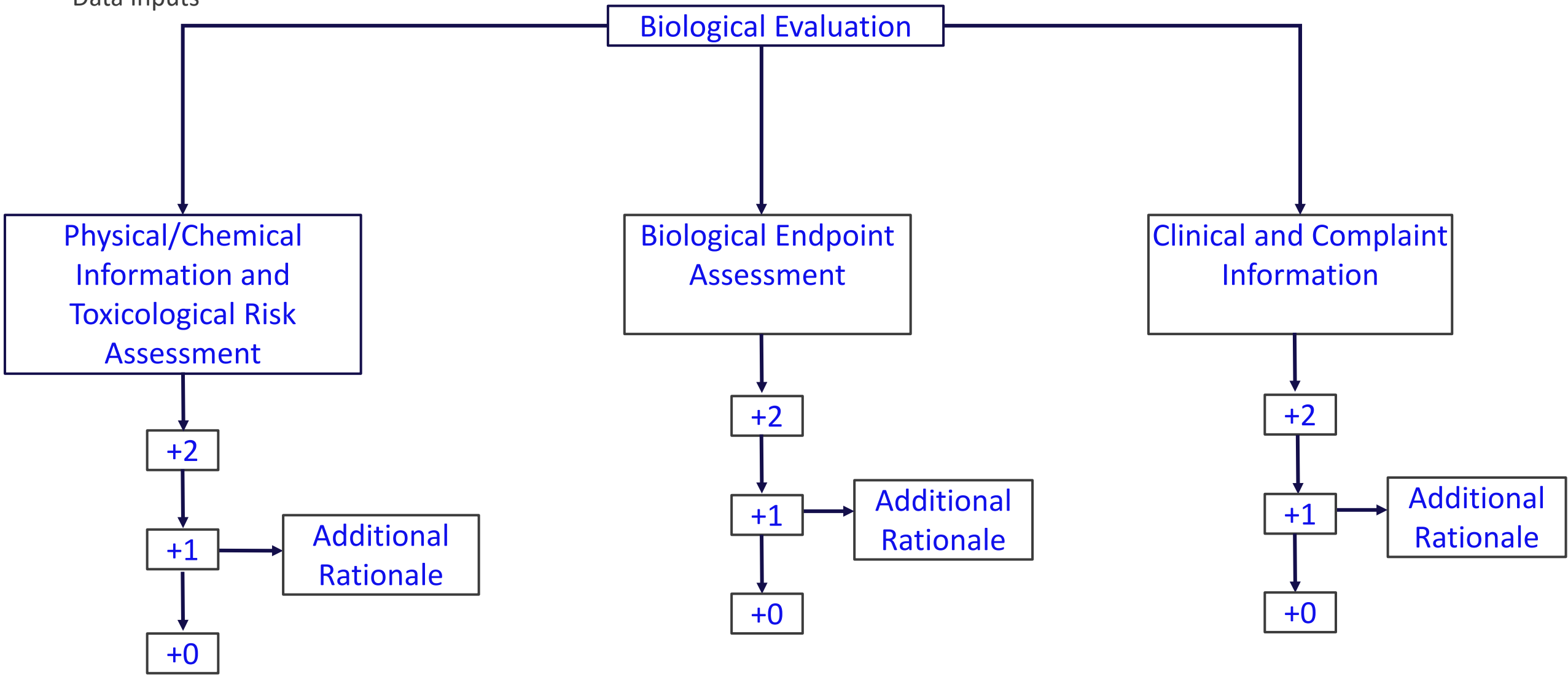
Weight-of-Evidence Framework

Data Inputs



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Weight-of-Evidence Framework

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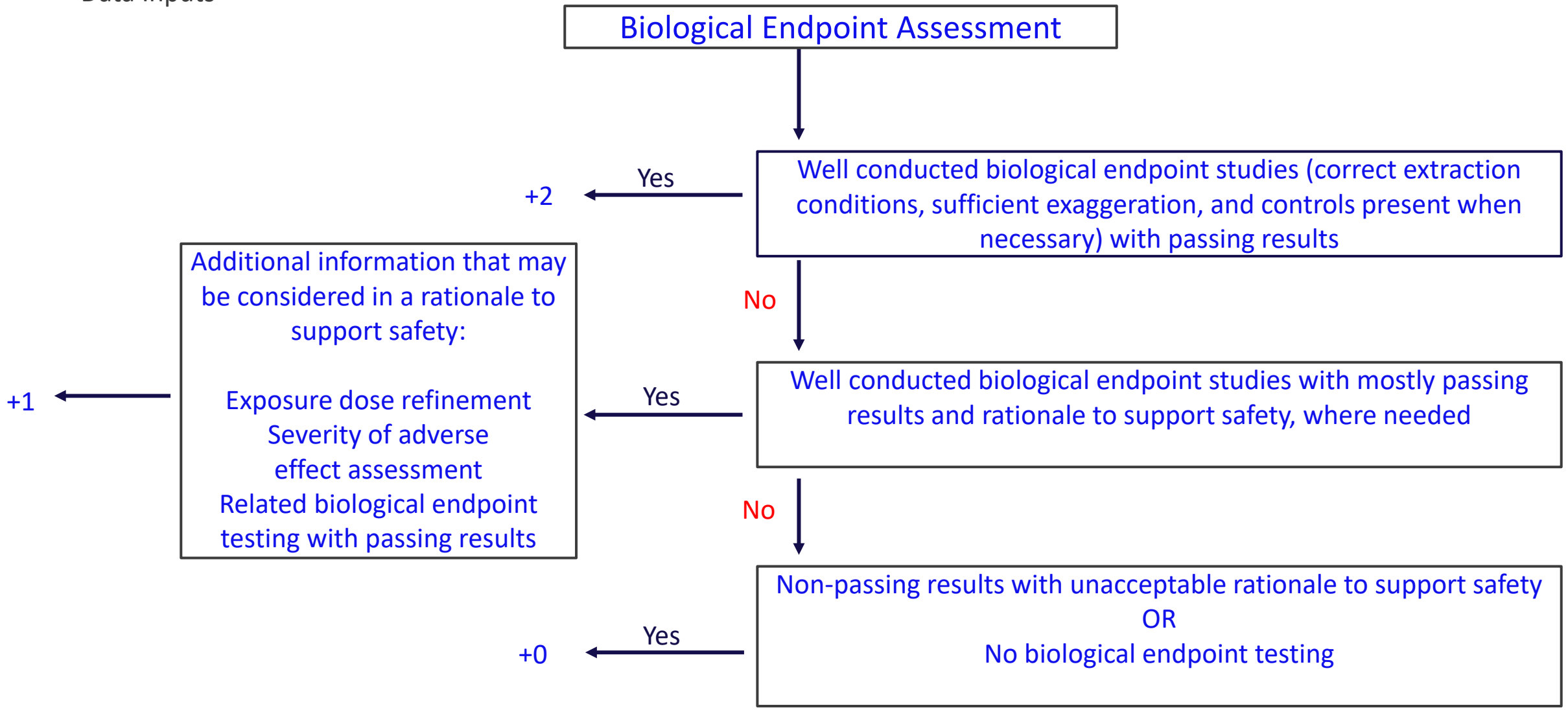

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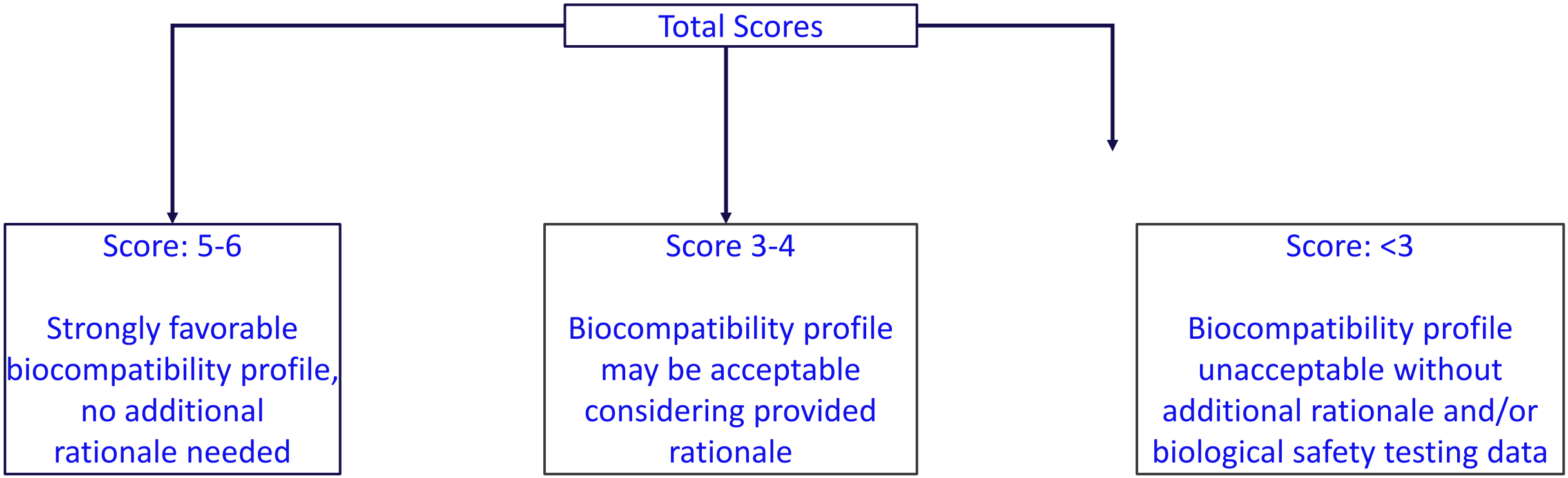
Weight-of-Evidence Framework

Total Scores



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Application of Weight-of-Evidence Framework

Case Study

- New Product.
  - Physical/Chemical Characterization and TRA.
    - Drawings, dimensions, and formulation information were provided, but supplier information proprietary.
    - Analytical chemical characterization and TRA conducted with all MOS above 1.
    - WoE framework score = +2.

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  - Biological Endpoint Assessment.
    - All endpoint testing per device categorization were completed per applicable standards and GLP.
    - All assays were considered passing and acceptable, except irritation.
      - No rationale could be initially provided.
    - WoE framework score = +0.

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      - No rationale could be initially provided.
    - WoE framework score = +0.
  - Clinical and Complaint Information.
    - Due to the device being new and no predicate available, no devices had been used in patients at the time of evaluation.
    - No clinical or complaint history was available.
    - WoE framework score = +0.

Application of Weight-of-Evidence Framework

Case Study

- New Product.
  - Total score: 2+0+0 = 2
  - Unfavorable biocompatibility profile.
  - Additional testing or rationale should be considered to ensure no irritation risks could occur in the clinical setting.

Application of Weight-of-Evidence Framework

Case Study

- New Product.
  - The device is short-term use resorbable implant.
    - Irritation testing conditions were altered to be more clinically relevant (50°C → 37°C) which reduced irritation response.
  - An implantation study was carried out using a clinically relevant scenario and no irritation was observed.
    - This was used to support no patient risk when used clinically.
  - WoE Total Score: 2+**1**+0 = **3**.

Summary
Weight-of-Evidence

- Biological evaluations should not exist in a vacuum.
  - Biocompatibility assessments should evaluate the totality of evidence to determine risk.
  - This WoE framework is intended to drive consistency within the biological evaluation process and subsequent regulatory review.
  - Similar to Annex A of ISO 10993-1, WoE is not intended to be a checklist for us to simply perform all of the testing.
    - It is a tool to establish a set of parameters around the issue of “how much data is enough?” to ensure patient safety has been addressed.

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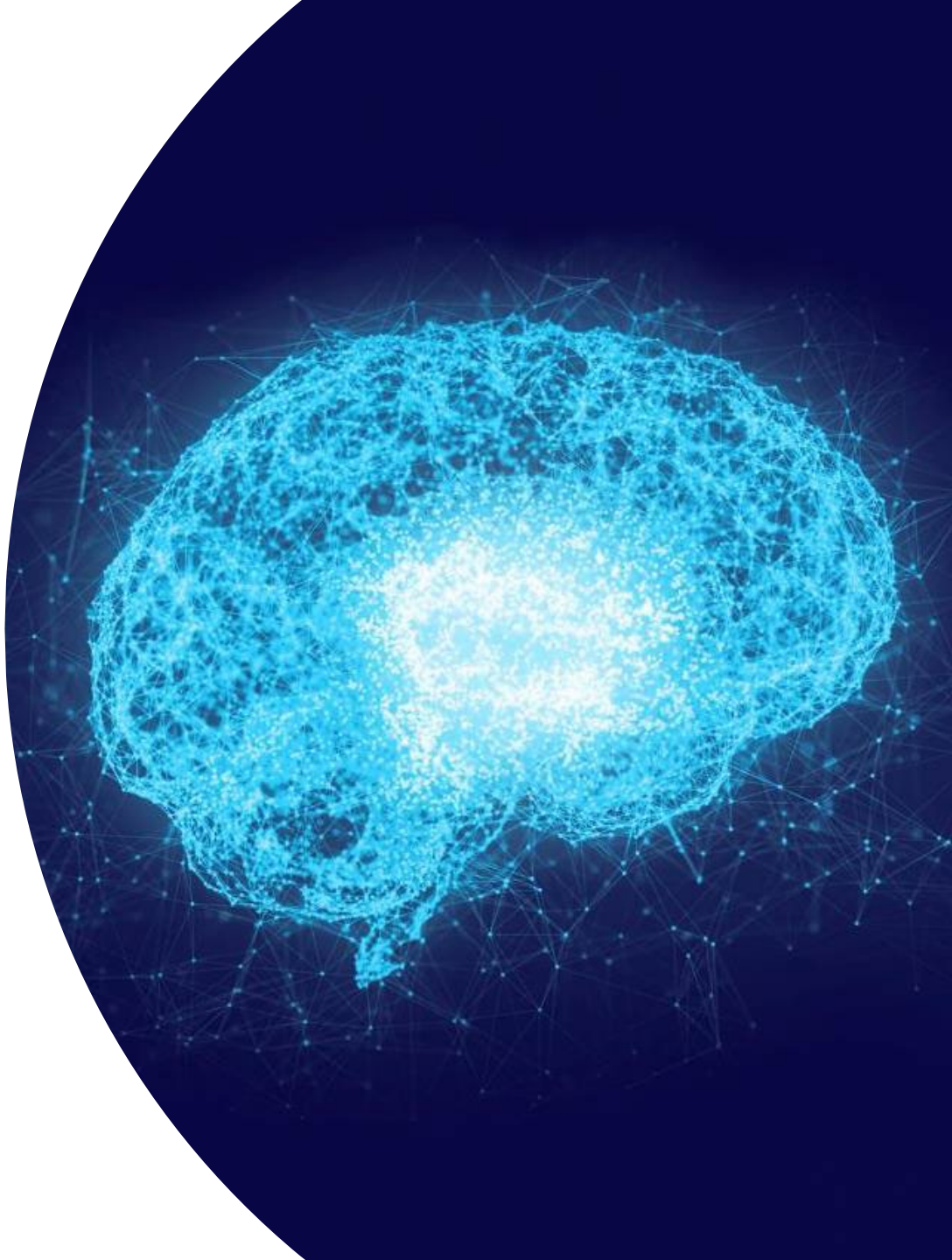

Thank you!

Contact Information

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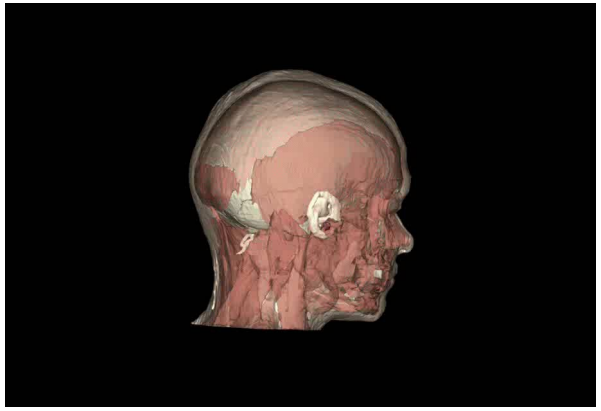

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CDRH Biocompatibility Thoughts

Ed Margerrison PhD
Director Office of Science and Engineering Labs
CDRH

Current Projects

- We are seeing the biggest challenges in chemical characterization
  - How to define the quality of chemistry?
    - Specifics calculations on UF, AET and others
  - How to show that a substitution/supplier change is acceptable
    - Pellethane polyurethanes
    - PFAS
    - New sterilization modes e.g. EtO to VHP
    - Many others
  - How can we standardize the Chem char/TRA approach?

The “Coverage Map” for NTA

- It is essential to be able to understand the breadth of detectability based on:
  - GC-MS LC-MS (and other) techniques and specific methods
  - The breadth of physicochemical properties of relevance, e.g.
    - Mw
    - Double Bond Equivalent
    - Boiling Point
    - pKa
    - logP
    - Refractive Index

CDRH Approach

- Define a chemical dataset that:
  - Covers a broad range of relevant physicochemical properties
  - Is readily available and relevant to E/L
- For Specific GC-MS and LC-MS conditions:
  - Measure the RRF compared with an internal reference
- Assess detectability across the breadth of the dataset
  - Compare RRFs at >= 3 concentrations
  - Look for detectability deserts = blind spots

The Chemicals List for Analytical Performance (CLAP)

- All this information is now publicly available through the CDRH RST App:
  - GC-MS LC-MS (and other) techniques and specific methods
  - The breadth of physicochemical properties of 106 easily sourced and relevant chemicals
    - Mw. 102 to 1178 g mol^{-1}
    - Double Bond Equivalent, -2 to 25
    - Boiling Point, 148 to 922 oC @ 760 mmHg
    - pKa, -9 to 18.25
    - logP, -0.7 to 23
    - Refractive Index, 1.289 to 1.757
  - https://cdrh-rst.fda.gov/chemicals-list-analytical-performance-clap
  - We want others to generate their own or use ours
    - One company has already repeated the first dataset with good agreement

The CDRH RST App

Regulatory Science Tools Catalog

Search Tool Catalog

Search

Tools Categories

- Lab Method (30)
- Computer Model (21)
- Dataset (6)
- Phantom (2)
  - Physical (1)
- Clinical Outcome Assessment (1)

Program Areas

- Cardiovascular (18)
- Medical Imaging and Diagnostics (13)
- Orthopedic Devices (8)
- Biocompatibility and Toxicology (6)
- Credibility of Computational Models (6)
- Materials and Chemical Characterization (6)
- Neurology (5)
- AI / Machine Learning (3)
- Medical Extended Reality (3)
- Patient Monitoring and Control (3)
- Electromagnetic and Electrical Safety (2)
- Human Device Interaction (2)
- Ophthalmology (2)

Mock Circulatory Loop to Generate Variable Adult Heart Conditions for Evaluating Mechanical Circulatory Support Devices

Lab Method

This regulatory science tool is a lab method tool used for simulating target clinical use patient conditions on the bench using a mock circulatory loop in conjunction with the ISO 14708-5 standard specifications for circulatory...

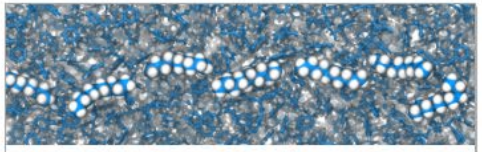
Cardiovascular

A Mock Circulation Flow Loop for Non-clinical Characterization of Pressure-Based Cardiac Output Monitoring Systems

Lab Method

This regulatory science tool is a lab method in the form of a physical mock circulation loop (MCL) used for simulating peripheral radial pressure waveforms.

Cardiovascular | Patient Monitoring and Control

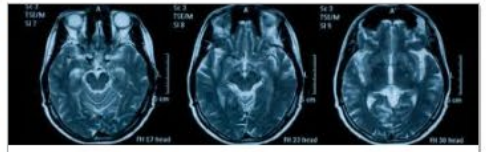


Extract Preparation for Chemical Characterization Studies – Liquid-liquid Extraction

Lab Method

This regulatory science tool is a model for establishing analyte recovery in chemical characterization studies following liquid-liquid extraction.

Materials and Chemical Characterization



BoneJ Headless: An Automated Python Tool for Bone Microstructure Analysis

Lab Method

This regulatory science tool is a lab method that computes bone microstructure metrics to characterize bone morphology and skeletal geometry.

Medical Imaging and Diagnostics

Line Spread Measurement Method on Head-Mounted Displays

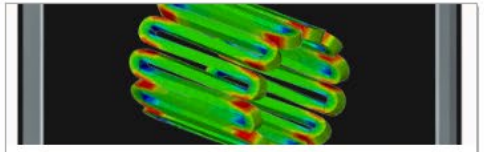
Lab Method

Radially Variant Contrast Measurement Method on VR Head-mounted Displays

Lab Method

MIC-MET Tree: Decision Tree for Medical Imaging AI/ML Classification Metrics

Lab Method

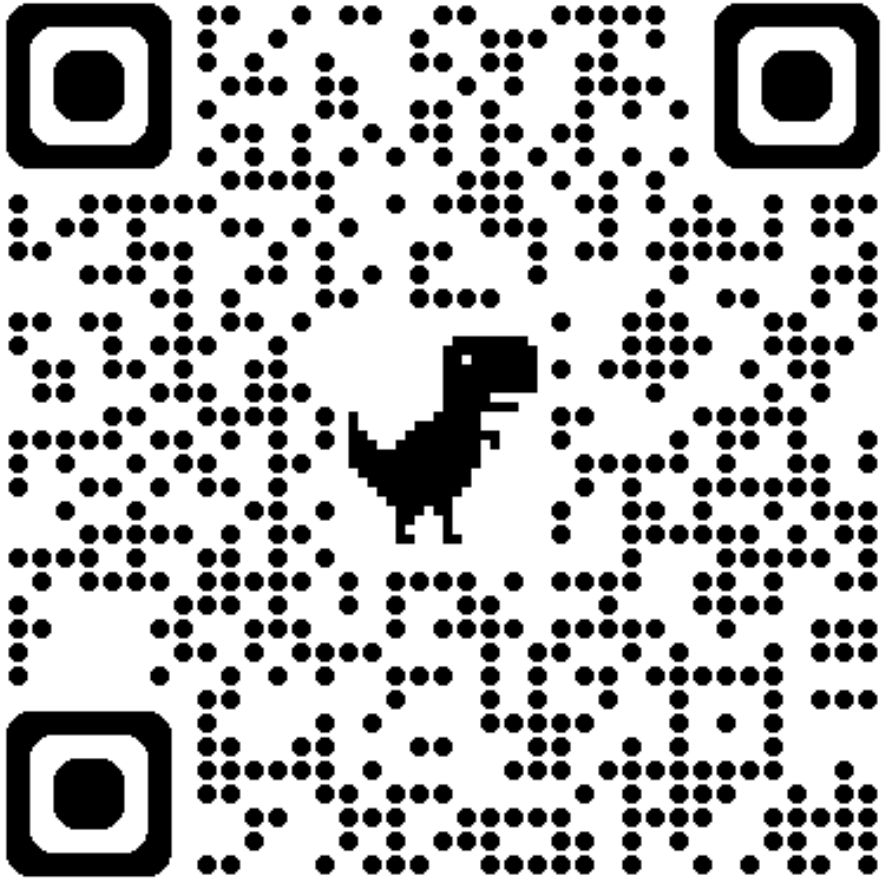


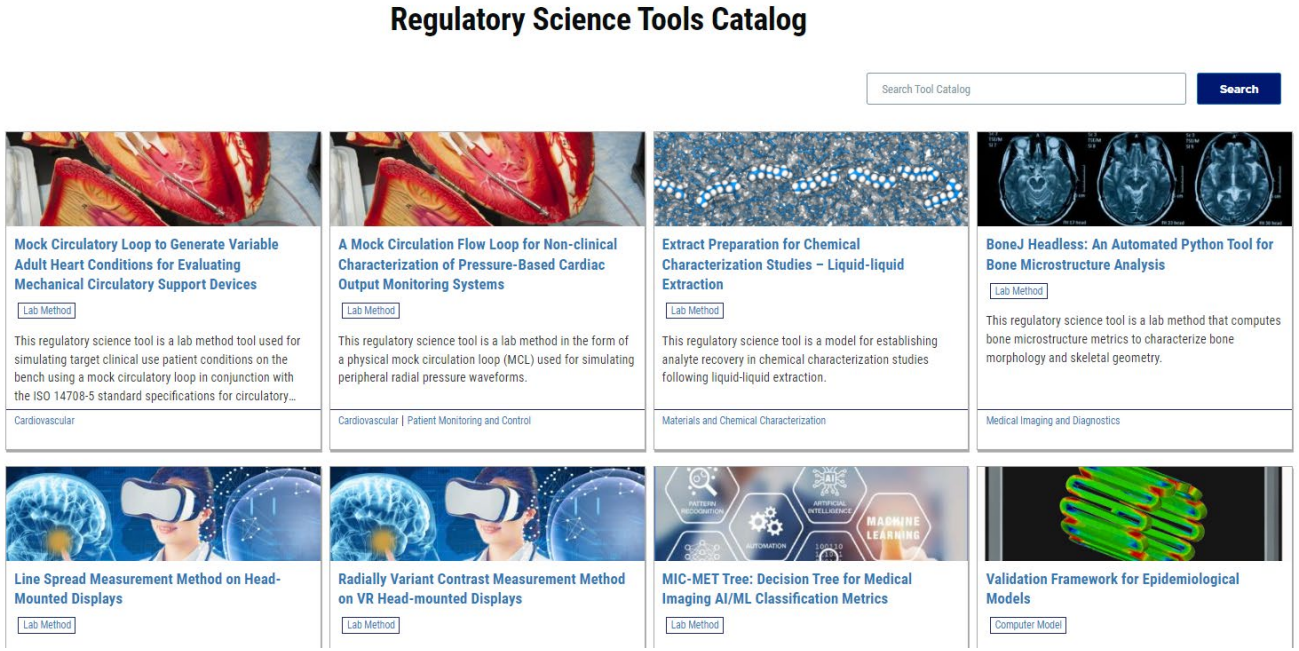
Validation Framework for Epidemiological Models

Computer Model

https://cdrh-rst.fda.gov/chemicals-list-analytical-performance-clap

The CDRH RST App



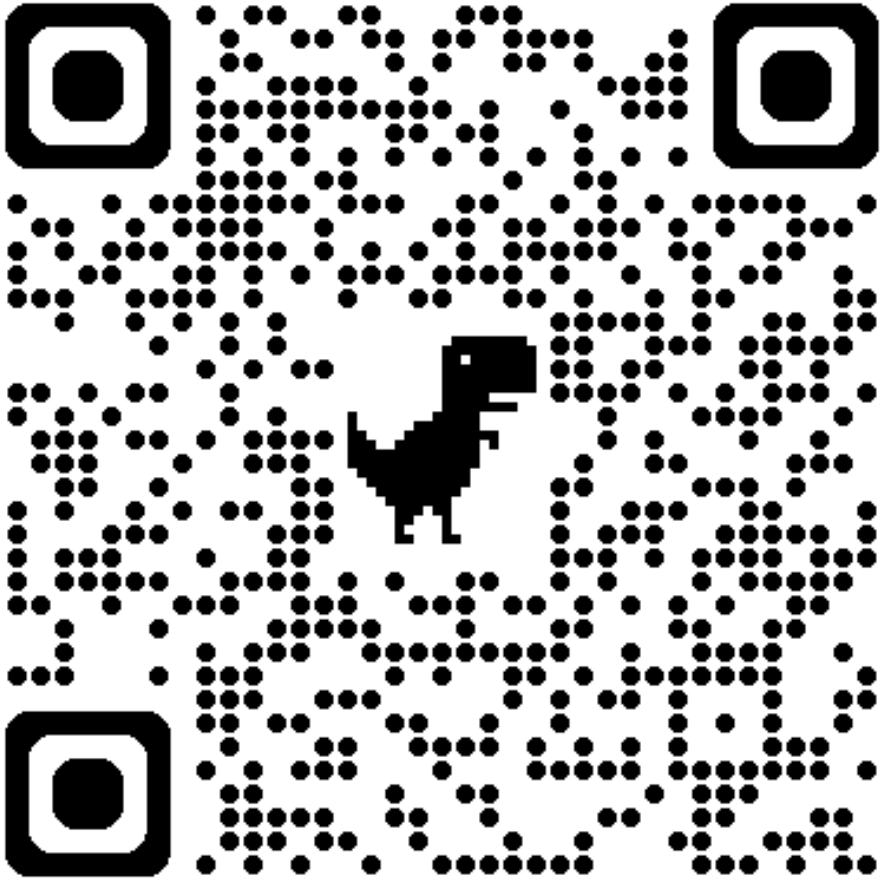


https://cdrh-rst.fda.gov/chemicals-list-analytical-performance-clap

Chemical Equivalence

- Another High Priority Area for CDRH
  - It's much more difficult to prove that two datasets are the same than it is to prove they are different
  - This will become increasingly important with:
    - Existing supplier changes, normal business
    - New challenges including PFAS and some changes in manufacturing sites of polyurethanes
  - One of our industry collaborations has been focused on E/L variability
    - Allows us to formulate a statistical understanding of equivalence
    - See Saylor and Young (2024) in Regul Toxicol Pharmacol DOI: 10.1016/j.yrtph.2024.105612
    - Focus now is to make it practical, it is the key to getting chem char into ASCA

Chemical Equivalence



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& DEVICES

QUESTIONS?

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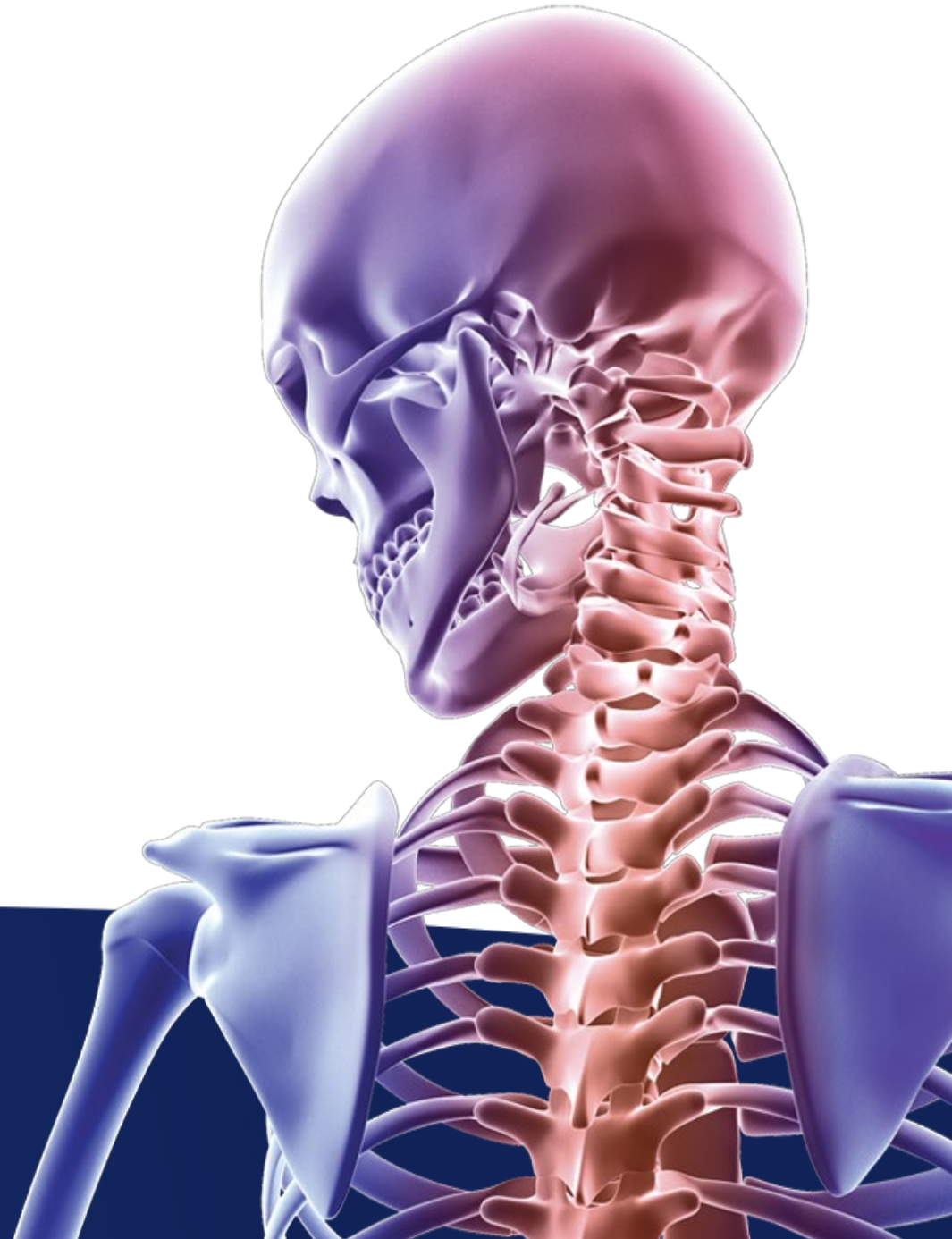

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FOR ATTENDING

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