Understanding Context of Use for New Approach Methods (NAMs) in Medical Device Evaluation: Case Studies

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U.S. Food and Drug Administration

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"Validation and Establishing Scientific Confidence in New Approach Methods (NAMs)" session

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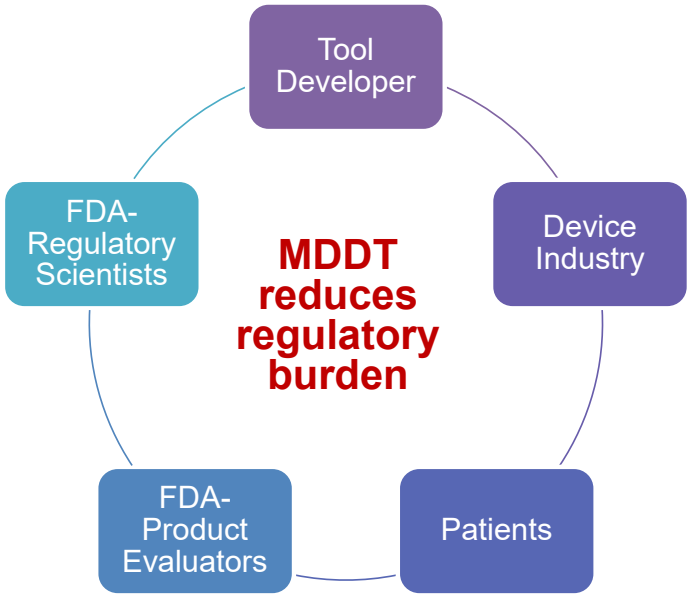
Overview

- FDA's Commitment to Alternative Methods
- CDRH's Medical Device Development Tools (MDDT) Program and Context of Use
- Considerations for Qualification of New Approach Methods for Biocompatibility Evaluation of Medical Devices
- Example Data Organization Template
- Resources

FDA Commitment to Alternative Methods

- FDA's 2020 Biocompatibility Guidance
  - "With the advancement of scientific knowledge regarding the basic mechanisms of tissue responses, FDA agrees with the ISO 10993-1:2009 revision focus on minimizing the 'number and exposure of test animals by giving preference to chemical constituent testing and in vitro models, in situations where these methods yield equally relevant information to that obtained from in vivo models.'" (Section IV-B)
- FDA's 2022 Advancing Regulatory Science at FDA: Focus Areas Of Regulatory Science (FARS): Increasing Choice and Competition through Innovation
  - Medical Product Development Tools: Novel Technologies to Improve Predictivity of Non-clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing
- FDA's Alternative Methods Working Group
  - Report "Advancing New Methodologies at FDA" (January 2021)
- FDA's Predictive Toxicology Roadmap (December 2017)

Medical Device Development Tools (MDDT) Program



- Voluntary program for tool developers
- Tool submitters: person, group, consortium, or organization (including FDA)
- Goal: To facilitate medical device innovation, development, and regulatory approval/clearance through qualifying and making MDDTs from tool developers, device industry, and other stakeholders publicly available

FDA Guidance "Qualification of Medical Device Development Tools" (2017)

What is an MDDT?

- **Medical Device Development Tool (MDDT)** is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device
  - A tool that is scientifically validated and qualified for a specific ***context of use*** (COU) for use in device development and to support regulatory decision-making

- **MDDT Type:** Non-clinical Assessment Model
  - A non-clinical test model or method that measures or predicts device function or in vivo device performance
  - Examples: in vitro models to replace animal testing, tissue phantoms to evaluate imaging devices, physics-based computational models

FDA Guidance "Qualification of Medical Device Development Tools" (2017)

Context of Use (COU)

- Description of the way the tool is to be used and the purpose of its use in medical device development, evaluation, and regulatory review process in a particular product area.

- An MDDT is qualified for a specific COU. The qualified COU defines the boundaries within which the available data adequately justify use of the MDDT.

- The COU should describe the specific role of the MDDT in device development. A complete COU should include:
  1. Tool or product area in which the MDDT is proposed to be qualified
  2. Specific output/measure from the MDDT
  3. Role of the MDDT in regulatory evaluation
  4. Phase(s) of medical device development in which tool measurements can be used (e.g., design evaluation, animal testing, clinical studies)

- As data are obtained from additional studies over time, tool developers may submit the supplementary data to the FDA to potentially expand upon the qualified COU.

FDA Guidance "Qualification of Medical Device Development Tools" (2017)
Medical Device Development Tools (MDDT) website: https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt

Considerations for Qualification of New Approach Methods for Biocompatibility Evaluation of Medical Devices

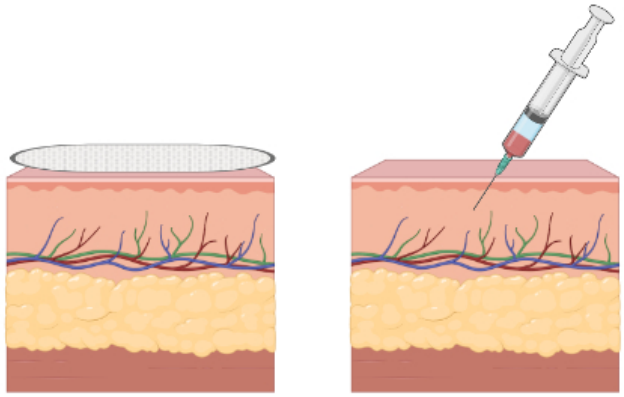
- Biocompatibility Endpoints and Tests
- Stand-Alone Assay vs. Integrated/Defined Approaches
- Mechanisms of Action and Test Outcomes
- Leveraging Existing Data
- Chemical Applicability Domain
- Qualification Testing Considerations

NAMs for Biocompatibility Evaluation of Medical Devices: Biocompatibility Endpoints and Tests

- What is the specific biocompatibility endpoint(s) being evaluated?
- Is there a specific biocompatibility test (or multiple tests) being proposed for replacement?

Example: Irritation (ISO 10993-23)

- Standard in vivo animal irritation tests
  - Dermal irritation
    - For medical devices that are contacting intact skin
  - Intracutaneous (intradermal) irritation
    - For medical devices that are contacting breached or compromised surface, externally communicating, or implants
- Human Skin Irritation Test
- Special Irritation Tests
  - Ocular, Oral Mucosa, Penile, Rectal, Vaginal



Dermal Irritation Intradermal Irritation

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NAMs for Biocompatibility Evaluation of Medical Devices: Biocompatibility Endpoints and Tests

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		
	Tissue+/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

Dermal Irritation Testing (Limited Contact with Intact Skin)

Dermal Irritation Testing (Repeat Patch) or Intracutaneous Irritation Testing

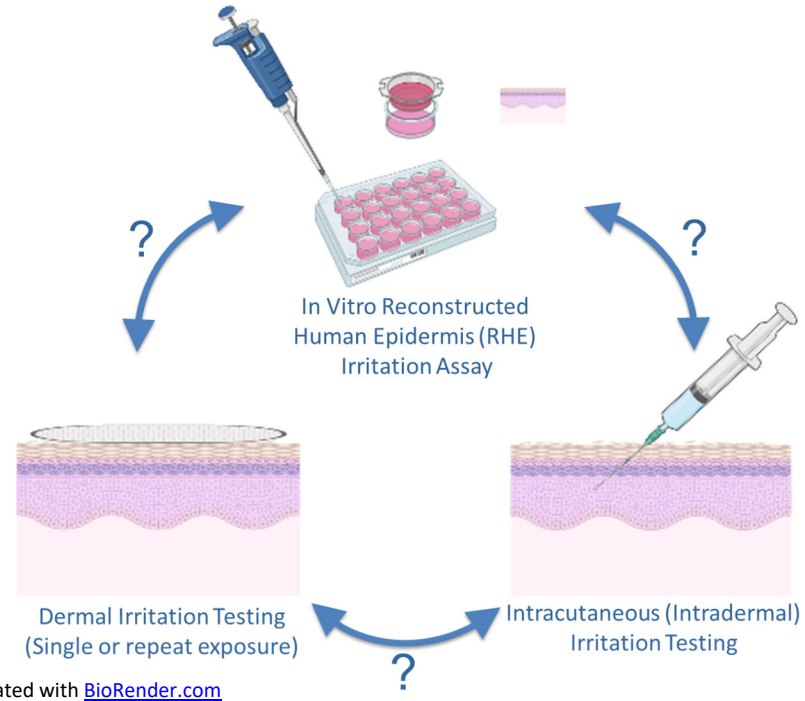
Intracutaneous (Intradermal) Irritation Testing

*Alternatively, special irritation tests (e.g., ocular, oral mucosal, penile, rectal, vaginal) relevant for medical devices intended to be applied to specific tissues

FDA 2020 Biocompatibility Guidance

ISO 10993-23:2021

NAMs for Biocompatibility Evaluation of Medical Devices: Biocompatibility Endpoints and Tests



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What is the proposed Context of Use?

Dermal Irritation Testing (Limited Contact with Intact Skin)

Dermal Irritation Testing (Repeat Patch) or Intracutaneous Irritation Testing

Intracutaneous (Intradermal) Irritation Testing

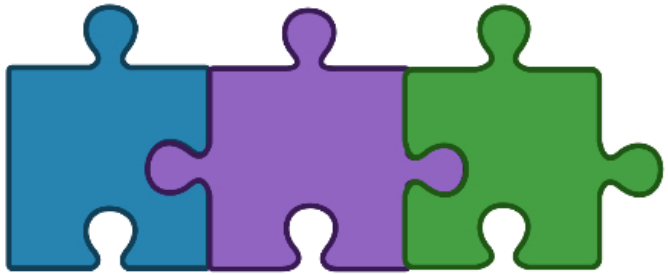
*Alternatively, special irritation tests (e.g., ocular, oral mucosal, penile, rectal, vaginal) relevant for medical devices intended to be applied to specific tissues

ISO 10993-23:2021

NAMs for Biocompatibility Evaluation of Medical Devices: Stand-Alone Assay vs. Integrated/Defined Approaches

- Is the tool intended to be used as a stand-alone assay or to provide supplementary data in conjunction with other information/tests?
  - Integrated Approaches to Testing and Assessment (IATA)
    - Defined Approaches (DA)

- Example: Skin Sensitization
  - Defined Approaches on Skin Sensitization
    - Organization for Economic Co-operation and Development (OECD) Guideline No. 497



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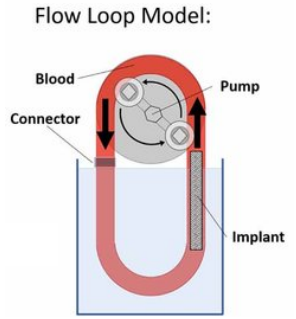
NAMs for Biocompatibility Evaluation of Medical Devices: Mechanisms of Action and Test Outcomes

- How do the *mechanisms of action* and/or the *biological endpoints* evaluated in the tests compare?
  - Proposed NAM
  - Currently used biocompatibility test

- How does screening with the proposed NAM address relevant *outcomes* from the currently used test?

Example: In Vitro and In Vivo Thrombogenicity

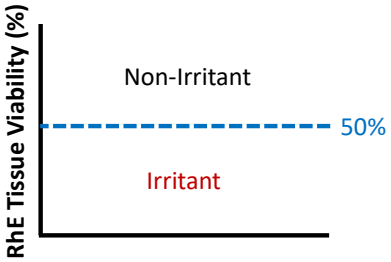


Theurer et al. 2021 Biomedical Materials

Thrombus formation score description	Score
No significant thrombosis (a very small clot is acceptable at insertion).	0
Minimal thrombosis, one location.	1
Minimal thrombosis, multiple locations.	2
Significant thrombosis, > 1/4 to ≤ 1/2 the surface of the implant, vessel patent.	3
Significant thrombosis, > 1/2 the surface of the implant, vessel patent.	4
Vessel completely occluded.	5

ISO 10993-4:2017

Example: In Vitro RhE Irritation and Dermal Irritation Testing



Erythema and edema scoring

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Table 3 — Primary or cumulative irritation index categories in a rabbit

Mean score	Response category
0 to 0,4	negligible
0,5 to 1,9	slight
2 to 4,9	moderate
5 to 8	severe

ISO 10993-23:2021

NAMs for Biocompatibility Evaluation of Medical Devices: Leveraging Existing Data

- What *qualification data* already exist for the proposed NAM?
  - Scientific literature (e.g., neat chemicals, medical device extracts)
    - Variability of in vivo data due to differences in animal model, administration protocols, duration and frequency of exposure(s)
    - Variability of in vitro data due to differences in test systems/models, test protocols (administration, exposure), biological endpoints
    - Variability of both in vivo and in vitro data due to differences in test article (e.g., dose, purity), preparation, vehicle, and administration
    - Neat chemicals (limited data on dilute concentrations and mixtures)
    - Testing on products usually does not include detailed chemistry/materials/manufacturing information
  - CDRH external stakeholder data

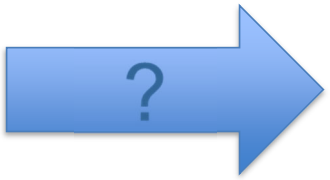
NAMs for Biocompatibility Evaluation of Medical Devices: Leveraging Existing Data

- How is the existing data relevant to support qualification of the proposed tool for biocompatibility evaluation of medical devices?
  - Is the identical tool being used and/or has the method been modified?
  - Are there multiple similar tests, and if so, does their performance differ?
  - Is the chemical applicability domain relevant to medical devices?
  - Is there in vitro-in vivo comparison data?
    - In vitro NAM vs. in vivo biocompatibility data (animal and/or human)
    - Identical test article?
  - How do known limitations of the assay, if applicable, impact the COU?
- What data gaps still need to be filled?
- For NAMs that have been validated for testing of neat chemicals, additional information may be needed to qualify the method for use in medical devices

NAMs for Biocompatibility Evaluation of Medical Devices: Leveraging Existing Data – Irritation Example

- OECD Test Guideline (TG) No. 439: "In Vitro Skin Irritation: Reconstructed Human Epidermis Test Methods" (June 2021)
  - Validated for neat chemicals with diverse range of physical-chemical properties using the United Nations (UN) Globally Harmonized System (GHS) Classification Category 2 (irritant) chemicals
  - Does not permit classification of chemicals to UN GHS Category 3 (mild irritant)
  - Consideration needed for testing of mixtures, difficult-to-test chemicals, or chemicals not clearly within the applicability domain in the TG

Validation with Neat Chemicals



Medical Device Extracts
- Unknown composition
- Dilute mixtures
- May include mild irritants

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NAMs for Biocompatibility Evaluation of Medical Devices: Leveraging Existing Data – Irritation Example

Validation with Neat Chemicals

Medical Device Extracts
- Unknown composition
- Dilute mixtures
- May include mild irritants

- Data needed to assess the applicability of the RhE irritation assay for biocompatibility evaluation of medical devices
  - Irritant chemicals with a range of potencies (including mild/moderate irritants)
  - Irritant chemicals representative of medical devices
  - Testing using medical device extraction techniques per ISO 10993-12
  - Testing using representative medical device materials (matrix interferences)
  - Testing using mixtures of chemicals
  - In vitro-in vivo correlation (human or animal data) from the same test article (e.g., chemical, concentration, purity)

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NAMs for Biocompatibility Evaluation of Medical Devices: Chemical Applicability Domain

- *Chemical applicability domain* relevant to medical devices (for chemical-based toxicity endpoints)
  - Chemicals with a range of potencies (e.g., weak, moderate, strong)
  - Chemicals representative of medical device materials/manufacturing
  - Chemicals with diverse range of physico-chemical properties relative to those in medical devices
  - Dilute concentrations
  - Mixtures

- Are there any chemicals or device materials/designs incompatible with the test system?
  - Example: Nanoparticles, specific chemical class

NAMs for Biocompatibility Evaluation of Medical Devices: Qualification Testing Considerations

- Modifications to the test protocol for medical device evaluation:
  - Test system suitability with *polar and non-polar device extracts*, if applicable
  - Optimization of *exposure duration* to increase test sensitivity
  - Use with *device extracts* versus *direct testing* on the device itself
  - Use with *large versus small surface area* devices

- For what *types of devices* can the proposed NAM be used? How does the qualification data support evaluation of these devices?
  - Durable and/or absorbable devices that include polymers, ceramics, metals, biologics, hydrogels, liquids, aerosols, nanomaterials, etc.

NAMs for Biocompatibility Evaluation of Medical Devices: Qualification Testing Considerations

- How can *control and test samples* be selected to confirm that the NAM can *distinguish between positive and negative responses*?
  - For example, can the NAM:
    - Distinguish between *weak/moderate toxicants* (e.g., for chemical-based toxicity endpoints)
    - Distinguish between positive and negative responses if there are *changes in design that could impact the biological response* (e.g., for endpoints like thrombogenicity where geometry and blood flow could impact thrombogenicity potential)

- Justification for the number and type of *test samples* used to support the specified context of use

NAMs for Biocompatibility Evaluation of Medical Devices: Qualification Testing Considerations

- Why is the performance (e.g., accuracy, sensitivity, specificity, reproducibility) of the NAM adequate for the proposed context of use?
  - If intended to replace an animal test, is the performance equivalent or better than the current in vivo biocompatibility test?
  - How does the NAM performance compare to clinical data, if available?

NAMs for Biocompatibility Evaluation of Medical Devices: Example Data Organization Template - Sensitization

The following tables summarize available information on positive and negative reference chemicals (both from the literature and from new data used to qualify the proposed methods)

Table 1 – Chemical properties

Chemical* Name	Chemical Identifier (CAS RN)	Physico/Chemical Properties and Chemical Reactivity							Is chemical a pre- or a pro-hapten? (Pre / Pro / Both / Neither / ND)	Data Source(s) (provide reference for all literature data, databases and/or computational models cited)
		Molecular Weight	LogP	Water Solubility	Melting Point	Boiling Point	Vapour Pressure	Chemical Reactivity Domain(s)#		
Chemical 1										
Chemical 2										
Chemical 3										
....										
...										

CAS RN = Chemical Abstract Services Registration Number; LogP = Partition Coefficient; ND = no data available

*Chemical is a positive or negative reference chemical that is present in known quantities in the positive or negative reference material or is spiked into an extract or vehicle.

#Chemical reactivity domain refers to the chemical protein binding alerts (e.g., acylation, Michael addition, SN2, SNAr, Schiff base formation) for skin sensitization per Supporting Document to the OECD Guideline 497 on Defined Approaches for Skin Sensitization: Series on Testing and Assessment, No. 336.

Goode, Jennifer. "Medical Device Development Tools (MDDTs) and Biocompatibility Considerations." New Approach Methodology Use for Regulatory Application (NURA) Conference: Use of NAMs for the Biological Safety Assessment of Medical Devices, 2 December 2021, Virtual. Conference Presentation.

NAMs for Biocompatibility Evaluation of Medical Devices: Example Data Organization Template - Sensitization

Table 2 – Comparative Summary Sensitization Data

NOTE: address all of the same chemicals in Table 1 and Table 2

	Chemical Sensitization Summary Information								
Chemical Name	**Human Sensitizer (Y / N / ND)**	**Guinea Pig Sensitizer (Y / N / ND)**	**LLNA Sensitizer (Y / N / ND)**	**Known/suspected sensitizer based on other information (name of in silico, in chemico, in vitro assay etc.)**	**Sensitization Class (GHS, other)**	**Sensitization Potency (none, weak, moderate, strong)**	**Non-sensitizing concentration and lowest sensitizing concentration from literature / NA (if non-sensitizer) / ND**	**List any sensitization tests known to be incompatible with chemical**	**Data Source(s) (provide reference for all literature data, databases and/or computational models cited)**
Chemical 1									
Chemical 2									
Chemical 3									
….									
…									

Y = yes; N= no; ND = no data available; GHS = Globally Harmonized System of Classification and Labeling of Chemicals; NA = not applicable; OECD = Organization of Economic Co-Operation and Development; AOP = Adverse Outcome Pathway

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NAMs for Biocompatibility Evaluation of Medical Devices: Example Data Organization Template - Sensitization

Table 3 - Comparative In Vitro Data for the Candidate Test Method

NOTE: address all of the same chemicals in Table 1 and Table 3

	In Vitro Sensitization Assay Testing (Medical Device Extracts) Test Method Name: Related OECD Test Guideline (TG): Modifications made to OECD TG method for medical device testing: Yes/No Key event of AOP assessed:					In Vitro Sensitization Assay Testing (Neat Chemicals) Test Method Name: OECD Test Guideline (TG): Key event of AOP assessed:					
Chemical Name	**Data available (Y / N), and if chemical is incompatible with test**	**Did the in vitro sensitization assay correctly classify the chemical? (TP, TN, FP, FN)**	**Lowest test concentration where correct response from in vitro test method achieved**	**Concentration(s) Tested and Test Media (e.g., vehicle or extract)**	**Results**	**Data available (Y / N), and if chemical is incompatible with test**	**Did the in vitro sensitization assay correctly classify the chemical? (TP, TN, FP, FN)**	**Lowest test concentration where correct response from in vitro test method achieved**	**Concentration(s) Tested and Test Media (e.g., vehicle or extract)**	**Results**	**Data Source(s) (provide reference for all literature data, databases and/or computational models cited)**
Chemical 1											
Chemical 2											
Chemical 3											
…											
…											

Y = yes; N= no; TP = true positive; TN = true negative; FP = false positive; FN = false negative

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NAMs for Biocompatibility Evaluation of Medical Devices: Example Data Organization Template - Sensitization

Table 4 – Comparative Human and In Vivo Non-Human Sensitization Data

NOTE: address all of the same chemicals in Table 1 should be addressed in Table 4

	Human Sensitization Data				Guinea Pig Data				
Chemical Name	**Data available (Y / N), and if chemical is incompatible with test**	**Test (e.g., HPPT / HRIPT)**	**Concentration(s) Tested and Test Media**	**Lowest concentration for positive and other results**	**Data available (Y / N), and if chemical is incompatible with test**	**Test (e.g., GPMT, Buehler)**	**Concentration(s) Tested for induction and challenge and Test Media**	**Lowest concentration (for induction and challenge) for positive and other results (e.g., grade, frequency)**	**Data Source(s) (provide reference for all literature data, databases and/or computational models cited)**
Chemical 1									
Chemical 2									
Chemical 3									
…									
…									

Y = yes; N= no; HPPT = human predictive patch test; HRIPT = human repeat insult patch test; GPMT = guinea pig maximization test

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NAMs for Biocompatibility Evaluation of Medical Devices: Example Data Organization Template - Sensitization

Table 5 – Comparative In Vivo Non-Human Sensitization Data, cont.

NOTE: address all of the same chemicals in Table 1 and Table 5

	LLNA Data				Other Non-Human Data				
Chemical Name	**Data available (Y / N), and if chemical is incompatible with test**	**Test (e.g., Radioactive LLNA test, LLNA:DA, LLNA:BrdU-ELISA, LLNA:BrdU-FCM)**	**Concentration(s) Tested and Test Media**	**EC_3 and other Results**	**Data available (Y / N), and if chemical is incompatible with test**	**Assay Information**	**Concentration(s) Tested and Test Media**	**Lowest concentration for positive and other results**	**Data Source(s) (provide reference for all literature data, databases and/or computational models cited)**
Chemical 1									
Chemical 2									
Chemical 3									
…									
…									

Y = yes; N= no; LLNA = local lymph node assay; ELISA = enzyme-linked immunosorbent assay; FCM = flow cytometry method; LLNA:DA = non-radioactive Adenosine 5'-triphosphate LLNA test; LLNA:BrdU-ELISA = non-radioactive 2-Bromodeoxyuridine-ELISA LLNA test; LLNA:BrdU-FCM = non-radioactive 2-Bromodeoxyuridine-FCM LLNA test;
EC3 = amount of chemical required to induce in the LLNA, a three-fold increase in lymph node cell proliferation compared with vehicle control values

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NAMs for Biocompatibility Evaluation of Medical Devices: Mechanisms for Interactions with CDRH

Potential NAM Developer Questions:

- Will a single NAM likely be sufficient to address an endpoint of interest for biocompatibility, or might a *battery of in vitro tests* be needed?
- How important is it to understand the *mechanism(s) of action* evaluated by a NAM, as mechanisms of action may not always be fully understood from animal studies or human outcomes?
- How does CDRH interpret the results from *animal testing* for a specific biocompatibility assessment? What are the *key outcomes*?
- Can CDRH use information from NAMs if *not MDDT-qualified*? (e.g., supportive evidence if medical device qualification information is provided)?

Mechanisms for Interactions with CDRH:

- **CDRH's Q-submission process**
- **MDDT Program (MDDT@fda.hhs.gov)**

Alternative Methods Resources

- **FDA's 2022 Advancing Regulatory Science at FDA: Focus Areas Of Regulatory Science (FARS)**
  https://www.fda.gov/media/161381/download
- **FDA's Alternative Methods Working Group**
  https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda
- **FDA's report "Advancing New Methodologies at FDA" (January 2021)**
  https://www.fda.gov/media/144891/download
- **FDA's Predictive Toxicology Roadmap (December 2017)**
  https://www.fda.gov/media/109634/download

MDDT Resources

- **MDDT Program & Qualified Tools**
  https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt
- **MDDT Guidance Document (August 2017)**
  https://www.fda.gov/media/87134/download
- **Proposal Phase Template**
  https://www.fda.gov/media/109056/download
- **Summary of Evidence and Basis of Qualification (SEBQ) Template**
  https://www.fda.gov/media/106994/download
- **Inquiries for information:** MDDT@fda.hhs.gov

Biocompatibility Resources

- **General FDA 2020 Biocompatibility Guidance**
  https://www.fda.gov/media/85865/download
- **FDA Biocompatibility Assessment Resource Center**
  https://www.fda.gov/medical-devices/premarket-submissions/biocompatibility-assessment-resource-center
- **21 CFR 58 Good Laboratory Practices for Nonclinical Laboratory Studies Regulations**
  https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58

Other Resources

- **Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program Guidance**
  https://www.fda.gov/media/114034/download
- **FDA Recognized Consensus Standards Database**
  www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
- **CDRH Learn**
  - **How to Study and Market Your Device: Standards**
  - **Specialty Technical Topics: Biocompatibility**
    www.fda.gov/training/cdrhlearn/default.htm

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Thank you! Questions?