Chemical Characterization/Risk Assessment Approach for Biocompatibility Assessment

Current Successes and Future Challenges

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Disclaimer

The information in this presentation does not represent the official position of the US FDA.

Biocompatibility assessment of devices takes into account multiple biological endpoints (e.g., cytotoxicity, irritation, sensitization)

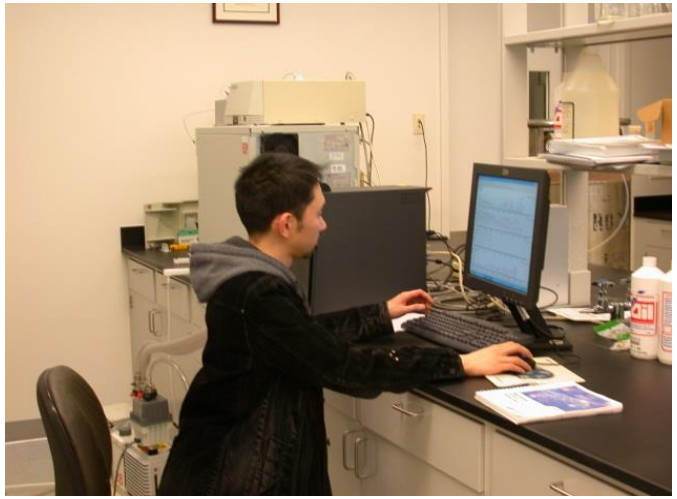
Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration 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@
Category	Contact														
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		

Approaches for the Biological Safety Evaluation of Medical Devices

Biocompatibility testing of extracts or intact device

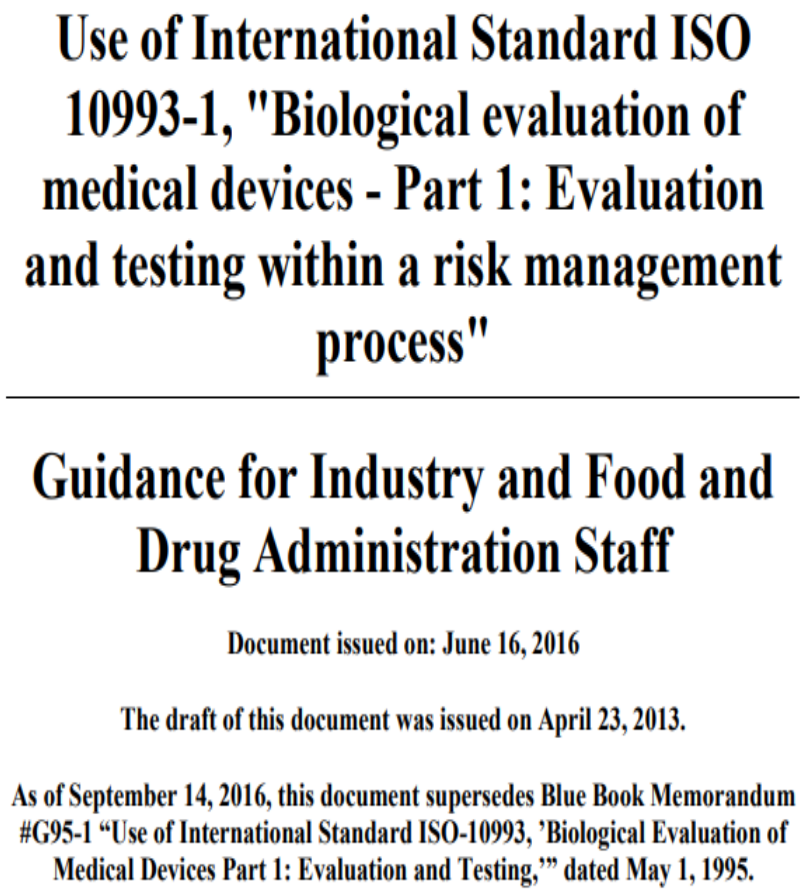
Chemical characterization/toxicological risk assessment



The US FDA is seeing an increasing number of submissions that use the chemical characterization/risk assessment approach to evaluate some endpoints in a biocompatibility evaluation strategy.

Current Successes

FDA Biocompatibility Guidance Document



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.

- Defines when the chemical characterization/risk assessment can be used in a biocompatibility assessment.
- Incorporates a number of cutting edge concepts (use of SAR modeling, TTC).
- Underscores the acceptance by FDA of qualified alternatives to biocompatibility testing in animals.

When is the Chemical Characterization/ Risk Assessment Approach Accepted (or Requested) by the US FDA?

FDA Biocompatibility Guidance (2016)

Section III. C. Considering Available Information to Identify and Mitigate Risks

- ***As an alternative to conducting systemic toxicity, genotoxicity, carcinogenicity, or developmental/reprotox tests (not other endpoints).***

Section VII. Chemical Assessment

- ***When the device contains compounds known to be toxic.***
- ***To evaluate the safety of absorbable/degradable or novel materials.***
- ***To explain positive results in biocompatibility tests.***

Current Successes

Chemical Characterization/ Risk Assessment Approach

Advantages

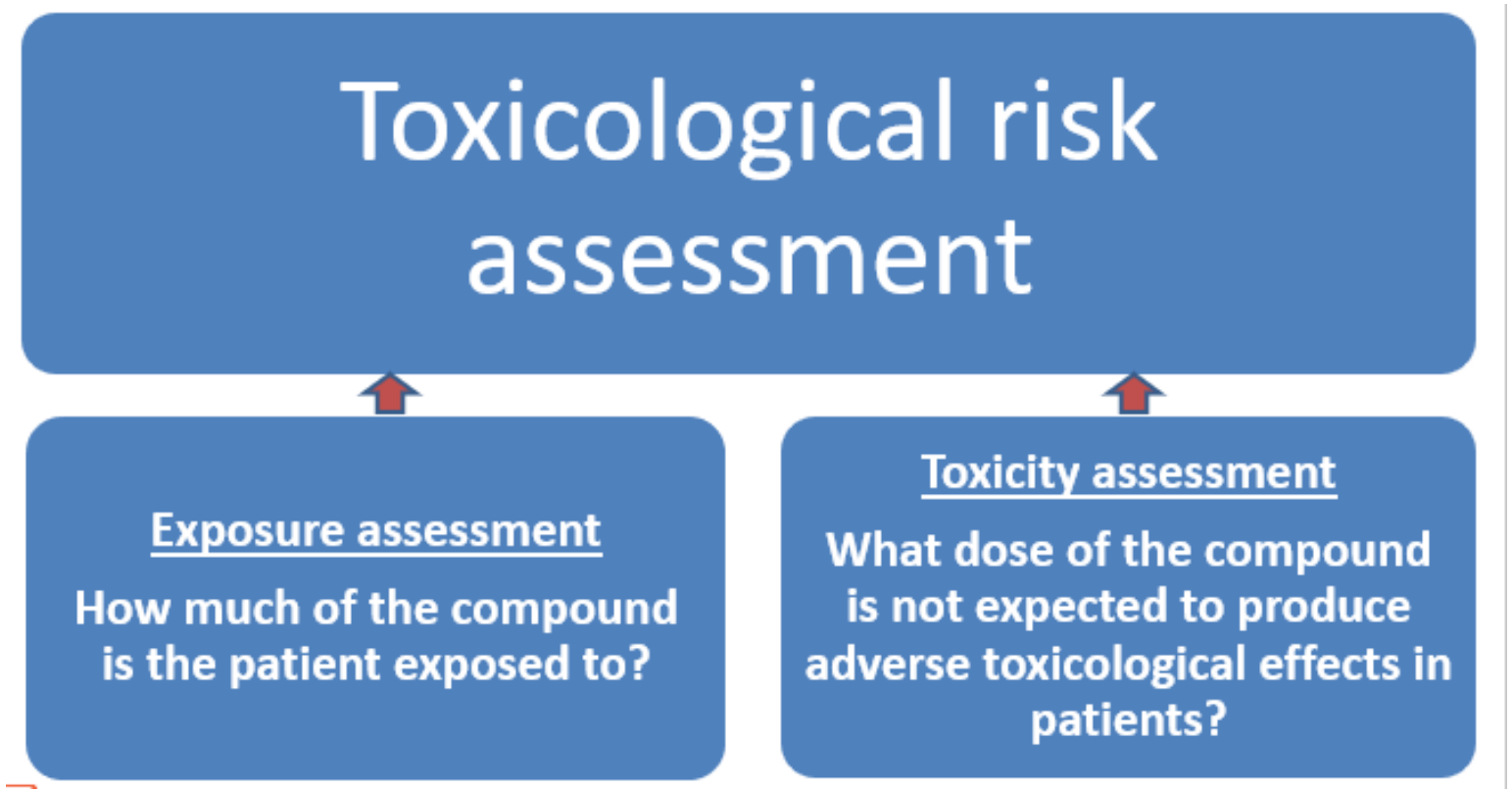
- May be more cost efficient, especially when used as an alternative to lengthy and costly bioassays.
- May reduce preclinical evaluation time for new devices and reduce animal use.
- Can be used to quickly assess potential toxicological risk associated with design, material, supplier, or processing change.

Challenges

- Chemical characterization is not a trivial process, requires considerable expertise.
- May require toxicity data (or default approach) for hundreds of compounds
- Requires expertise and a new skill set beyond typical biocompatibility assessment.

Current Successes

Revision of ISO 10993-17 and -18



ISO 10993-17 and -18 **ISO 10993-17**

Both standards are currently undergoing revision

Current Successes

TTC and AET

Implementation of the chemical characterization/risk assessment approach would not be possible without the use of the TTC concept

Chemistry

Allowed us to develop an analytical threshold (AET) for the identification and quantification of toxicologically relevant compounds.

Toxicity

Allowed us to develop science-based default TI values to use when toxicity data do not exist to derive the TI.

Future Challenges

Additional guidance and training in this area is needed to reduce regulatory uncertainty and to ensure that the regulated industry is preparing high-quality chemical analyses and toxicological risk assessments.

Chemistry/Exposure

- Address variability and uncertainty in chemical characterization steps.
- Provide clinically relevant exposure estimates.

Toxicity

- Develop consensus TIs
- Identify best practices for the use of *in silico* models
- Continue efforts to qualify alternative methods.

Future Challenge

Address uncertainty and variability in chemical characterization

- From a toxicological perspective, much of the uncertainty in the chemical characterization step is associated with the large number of structurally unidentified compounds in the extract.
- This makes the toxicological risk assessment step difficult or results in the use of conservative default assumptions.

Future challenge

Address uncertainty and variability in chemical characterization

Variation in Chemical Characterization Results from Four Test Laboratories

Monica Posgai, Johnson & Johnson, 2018 Society of Toxicology Annual Meeting

For example, the reported number of elements in the polyurethane water extract ranged between 0 and 12 for the four labs. For the polyisoprene isopropyl alcohol extract, the reported number of gas chromatography-mass spectrometry compounds ranged between 12 and 156 for the four labs.

This study into inter-laboratory comparisons revealed considerable quantitative and qualitative differences among chemical characterization results, which can potentially impact the outcome of a risk assessment.

Future Challenge

Provide clinically relevant estimates of exposure

Problem

- Data are often not available on the rate at which leachable compounds are released from devices. As a default, the assumption is made that either:
- The total amount of each compound in the device is released in one day (typically results in overestimate of daily dose), or
- The total amount of each compound is released linearly over the lifetime of the device (typically results in underestimate of daily dose).

Future Challenge

Provide clinically relevant estimates of exposure

Proposed solutions

- **Simple approach: Need more clinically relevant default assumptions for the rate at which leachable compounds are released from different types of polymers**

- **Use computational approaches to predict release kinetics:**

https://www.fda.gov/MedicalDevices/ScienceandResearch/ResearchPrograms/ucm477410.htm

Use of computational models to predict patient exposure to additives in polymers and metals (e.g., nickel) released from metallic implants

Annals of Biomedical Engineering
January 2018, Volume 46, Issue 1, pp 14–24 | Cite as

Conservative Exposure Predictions for Rapid Risk Assessment of Phase-Separated Additives in Medical Device Polymers

Authors | Authors and affiliations

Vaishnavi Chandrasekar, Dustin W. Janes, David M. Saylor, Alan Hood, Akhil Bajaj, Timothy V. Duncan, Jiwen Zheng, Irada S. Isayeva, Christopher Forrey, Brendan J. Casey

ELSEVIER

Acta Biomaterialia
Volume 70, 1 April 2018, Pages 304-314

Full length article

Predicting patient exposure to nickel released from cardiovascular devices using multi-scale modeling

David M. Saylor, Brent A. Craven, Vaishnavi Chandrasekar, David D. Simon, Ronald P. Brown, Eric M. Sussman

Future Challenges

Additional guidance and training in this area is needed to reduce regulatory uncertainty and to ensure that the regulated industry is preparing high-quality chemical analyses and toxicological risk assessments.

Chemistry/Exposure

- Address variability and uncertainty in chemical characterization steps.
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Toxicity

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- Continue efforts to qualify alternative methods.

Future Challenge

Harmonize requirements for toxicological risk assessment

Problem

- The quality of toxicological risk assessments provided in regulatory dossiers is highly variable.
- Regulatory agencies do not uniformly assess the adequacy of risk assessments provided in regulatory submissions.

Proposed solutions

- Revise and publish ISO 10993-17 and -18.
- Provide training on how to prepare toxicological risk assessments that will be accepted by regulatory agencies and third party assessors.

Future Challenge

Harmonize requirements for toxicological risk assessment

Problem: Variability in Tolerable Intake values for the same compound

- **TI values for a given compound can be derived using different toxicity data sets and Uncertainty Factors.**

Proposed solution: Develop a database of consensus TI values for commonly encountered E&L compounds

- **Promote uniformity in decision-making,**
- **Increase confidence in derived values,**
- **Result in more efficient use of resources, and**
- **Reduce time/cost needed to prepare each risk assessment.**

Future challenge

Regulatory acceptance of *in silico* predictions of toxicity

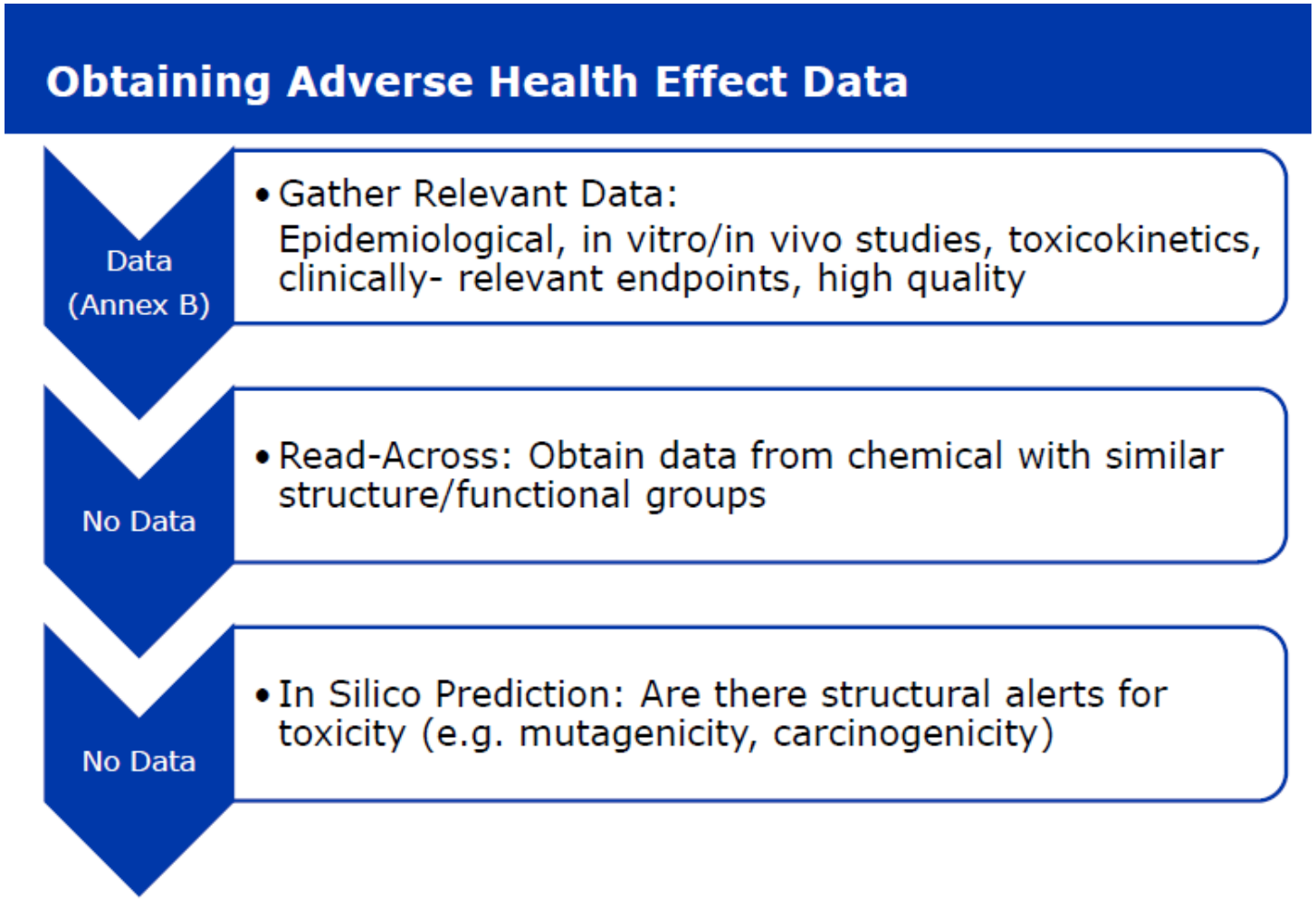
Problem

- **Toxicity data are not available for many compounds released from device materials.**

Solutions

- **Use TTC as a default TI**
- **Use computational models (e.g., structure-activity relationship models) to select an appropriate TTC**
- **Use computational models (e.g., Read Across) identify NOAEL values to serve as basis for the TIs.**

Proposed Approaches Outlined in ISO 10993-17 (draft revision) to Derive Default TI Values in the Absence of Compound-Specific Toxicity Data



Slide used with permission of Dr. Sherry Parker, Fresenius Medical Care

Role of SAR Modeling when the Chemical Characterization /Risk Assessment Approach is Used

From CDRH Biocompatibility Guidance:

In the absence of experimentally derived carcinogenicity information, structure activity relationship (SAR) modeling for these materials may be needed regardless of the duration of contact, to better understand the carcinogenicity potential for these materials.

- **SAR models are typically used to determine which TTC value is appropriate to use as a default TI value for the compound:**
  - **Possible carcinogen: Use cancer-based TTC value**
  - **Not likely to be carcinogen: Use noncancer TTC value**

Use of QSAR models and Read Across approaches to predict toxicity for data-poor compounds may not be universally accepted by all regulatory agencies and Notified Bodies

Future challenge

Regulatory acceptance of *in silico* predictions of toxicity

Proposed Solutions

- **Provide initial guidance in ISO 10993-17 on how to use *in silico* models to predict toxicity.**
- **Develop best practices for the use of computational approaches for the biological safety assessment of medical devices.**

Future Challenge

Consider a hybrid *in* silico-in vitro approach to predict toxicity

- **Proposal: Consider a hybrid approach that takes into account *in silico* prediction of genotoxicity/carcinogenicity of extractables and *in vitro* genotoxicity testing of an extract of the device.**
- **What should we do when the results of the *in silico* prediction *and in vitro* genotoxicity assay of the extract don't agree?**

From ICH M7: An appropriately conducted negative bacterial mutagenicity assay (Note 2) would overrule any structure-based concern, and no further genotoxicity assessments would be recommended (Note 1). These impurities should be considered non-mutagenic (Class 5 in Table 1).

		In Vitro Genotoxicity	
		POS	NEG
In Silico Prediction	POS	POS	NEG
	NEG	POS	NEG

Future Challenge

Adopt hybrid approach to predict genotoxicity/ carcinogenicity

Proposed approach may result in a small amount of additional testing (e.g., Ames test of an extract of the device), but would:

- **Provide increased confidence in genotoxicity/carcinogenicity predictions,**
- **Account for potential interactive effects among compounds extracted from device, and**
- **Represent a practical way to deal with Margin of Safety values < 1 when conservative cancer-based TTC values are used as the basis for the default TI.**

This approach does not necessarily represent current FDA policy.

FDA Biocompatibility Guidance (2016)

Future Challenges

Regulatory Acceptance of Alternative Approaches

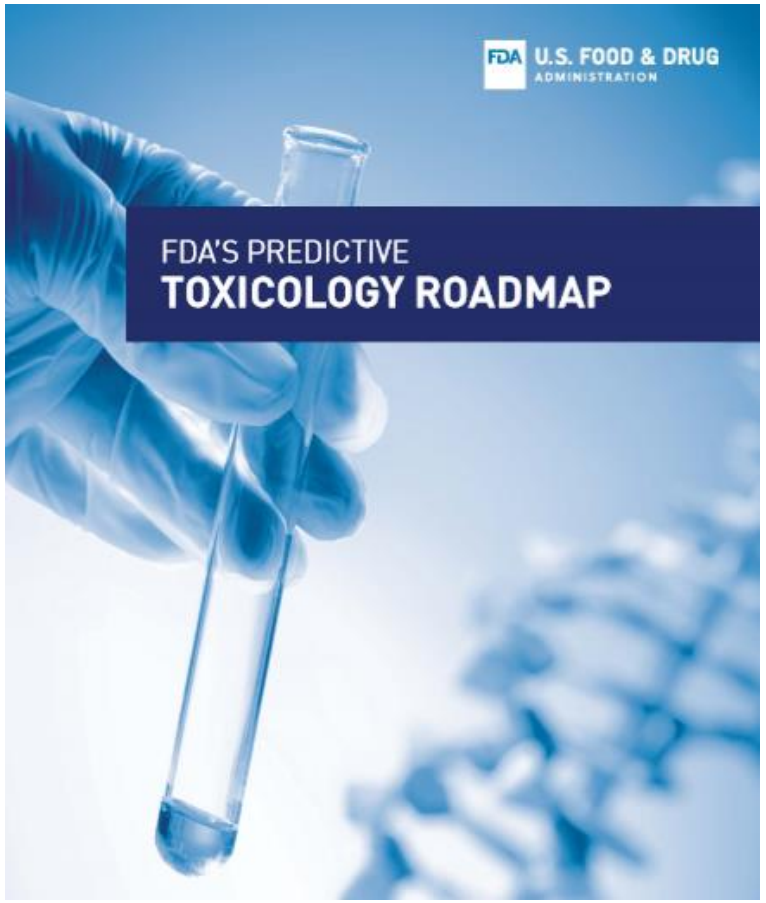
"…FDA agrees with the ISO 10993-1:2009 revision focus on minimizing the "number and exposure of test animals by **giving preference to chemical constituent testing and *in vitro* models**, in situations where these methods yield equally relevant information to that obtained from *in vivo* models."

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

Future Challenges

Regulatory Acceptance of Alternative Approaches

FDA Predictive Toxicology Roadmap (2018)



- Foster the development and evaluation of emerging toxicological methods and new technologies, and
- Incorporate these methods and technologies into regulatory review, as applicable.

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM587831.pdf

Future Challenges

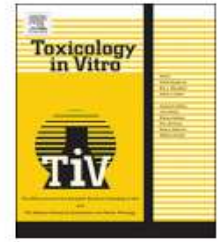
Methods to Validate *In Vitro* Methods for the Biocompatibility Assessment of Device Extracts

Toxicology in Vitro 50 (2018) 439–449

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit



Round robin study to evaluate the reconstructed human epidermis (RhE) model as an in vitro skin irritation test for detection of irritant activity in medical device extracts

Wim H. De Jong[a,*], Sebastian Hoffmann[b], Michelle Lee[c], Helena Kandárová[d], Christian Pellevoisin[e], Yuji Haishima[f], Beau Rollins[g], Austin Zdawczyk[h], Jamin Willoughby[i], Michael Bachelor[j], Timothy Schatz[k], Shelby Skoog[l], Sherry Parker[m], Anita Sawyer[n], Paolo Pescio[o], Kristina Fant[p], Kwang-Mahn Kim[q], Jae Sung Kwon[q], Helge Gehrke[r], Hana Hofman-Hüther[r], Marisa Meloni[s], Conrad Julius[t], Damien Briotet[u], Silvia Letasiova[d], Reiko Kato[f], Atsuko Miyajima[f], Liset J.J. De La Fonteyne[a], Christelle Videau[e], Carine Tornier[e], Audrey P. Turley[c], Nicholas Christiano[v], Thor S. Rollins[c], Kelly P. Coleman[w]

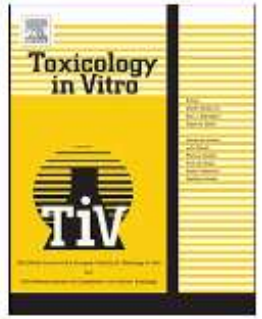
Staff from Nelson Labs have played an important role in the validation of this method

Toxicology in Vitro 50 (2018) 426–432

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit



Assessment of test method variables for *in vitro* skin irritation testing of medical device extracts

Daniel S. Olsen, Michelle Lee, Audrey P. Turley*

Nelson Laboratories, LLC, Salt Lake City, UT, USA

Medical Devices

Home > Medical Devices > Science and Research (Medical Devices) > Medical Device Development Tools (MDDT)

Medical Device Development Tools (MDDT)

Medical Device Development Tools (MDDT)

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The FDA's Medical Device Development Tools (MDDT) program is a way for the FDA to qualify tools that medical device sponsors can use in the development and evaluation of medical devices.

Qualification means that the FDA has evaluated the tool and concurs with available supporting evidence that the tool produces scientifically-plausible measurements and works as intended within the specified context of use.

https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/

Summary

Current Successes

1. Chemical characterization/risk assessment approach is becoming increasingly accepted by regulatory agencies (e.g., US FDA).
2. Revision of the ISO 10993-17 and -18 standards will address many of the outstanding issues.
3. Practical application of this method is possible through acceptance of TTC concept and use of TTC to establish AET and default TI values.

Do you think the Chemical Characterization/Risk Assessment approach has been successful as a means to improve the efficiency of the biocompatibility evaluation process?

Summary

Future Challenges

Additional guidance and training in this area is needed to reduce regulatory uncertainty and to ensure that the regulated industry is preparing high-quality chemical analyses and toxicological risk assessments.

Chemistry/Exposure

- Address variability and uncertainty in chemical characterization steps.
- Provide clinically relevant exposure estimates.

Toxicity

- Develop consensus TIs
- Identify best practices for the use of *in silico* models
- Continue efforts to qualify alternative methods.

What challenges do you see associated with the successful implementation of the Chemical Characterization/Risk Assessment approach?

Implications for CROs and clients

- Since many regulatory agencies and Notified Bodies are currently accepting the chemical characterization/risk assessment approach as an alternative to biocompatibility testing for some endpoints (e.g., systemic tox), this method provides another tool to develop a biocompatibility evaluation strategy for your device. In some cases, this approach may result in lower testing costs and reduced testing time.

- However, enhanced capabilities are needed to successfully implement this approach. Successful completion of the chemical analysis and preparation of the toxicological risk assessment will reduce the time needed for regulatory review of preclinical data in submitted dossiers.