Human Body Meets Medical Device – Are We Biocompatible?

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OCTOBER 13, 2018

[redacted] Mesh Lawsuits

by Ronald V. Miller, Jr.

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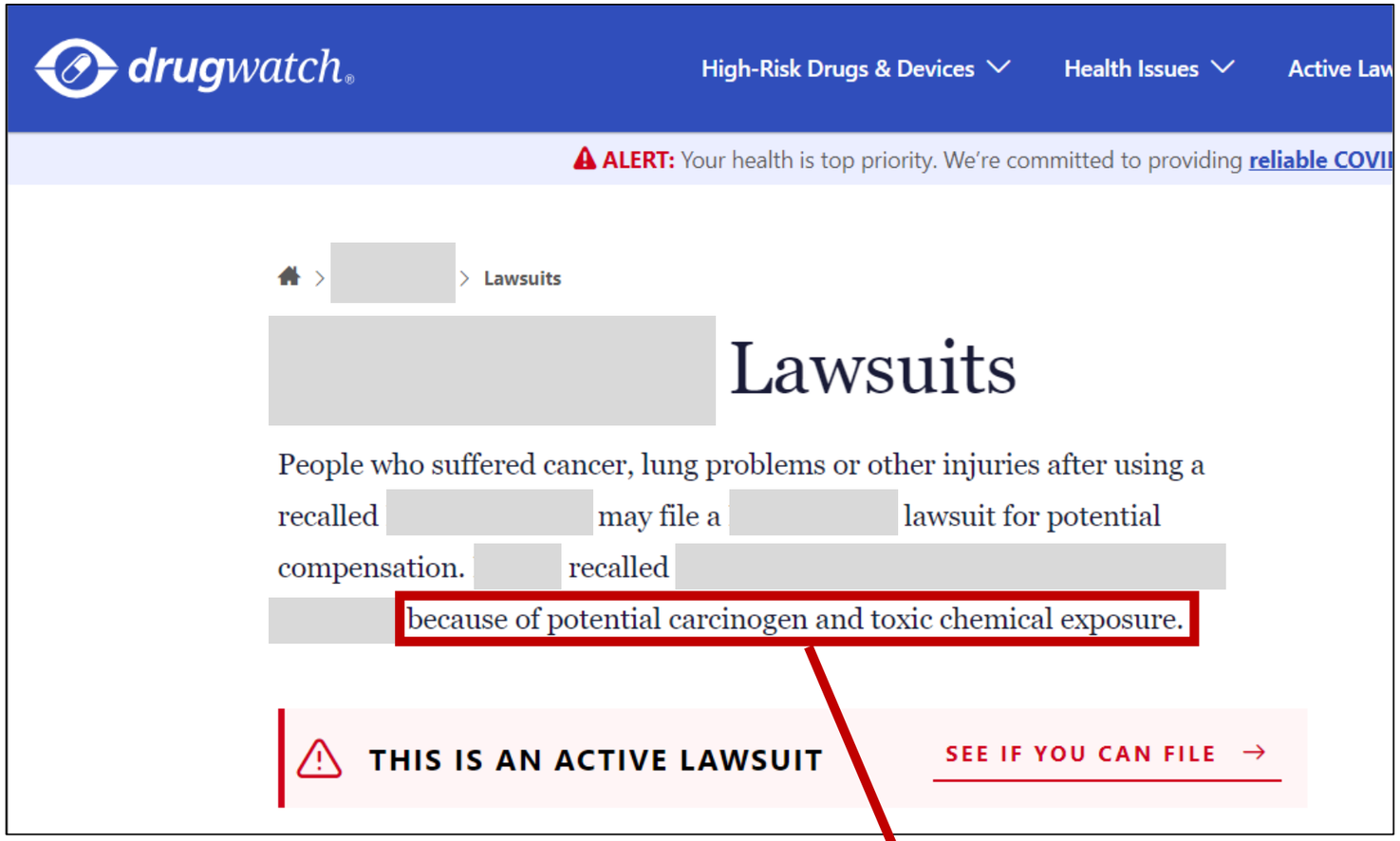
We have been getting a lot of calls from [redacted] hernia mesh victims. These poor people have a lot of questions and concerns and we try to lay some of those out for you here.

What are Hernia Mesh & Patch Devices?

A hernia is where tissue or organs in the abdominal area push out through a tear or defect in the abdominal muscle wall. Mesh and patch devices, such as the [redacted] products, are implanted during hernia surgery to strengthen and reinforce the muscle wall. Once implanted in the body, tissue will grow around the mesh. This means the devices must be inert or biocompatible to avoid rejection by the body. Like all surgical implants, they also

an insert or liner made of plastic, ceramic or metal. The implants used in hip replacement are or should be biocompatible (meaning they're designed to be accepted by your body) and made to resist corrosion, degradation and wear.

As a total hip joint replacement replaces the ends of both bones in a damaged hip joint to create new joint surfaces and a total hip replacement surgery replaces the upper end of the thighbone (femur) with a metal ball and resurfaces the hip socket in the pelvic bone with a metal shell and plastic liner, it is essential that the hip implants are biocompatible and are correctly made to resist corrosion, degradation, and wear as well as to work well without rubbing.



because of potential carcinogen and toxic chemical exposure.

FDA U.S. FOOD & DRUG ADMINISTRATION

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The FDA Requests [redacted] Voluntarily Recall [redacted] Textured Breast Implants and Tissue Expanders from the Market to Protect Patients: FDA Safety Communication

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← Home / Medical Devices / Medical Device Safety / Letters to Health Care Providers /

UPDATE: Potential Biocompatibility Concerns with [redacted] Orthopedics' [redacted] Devices - Letter to Health Care Providers

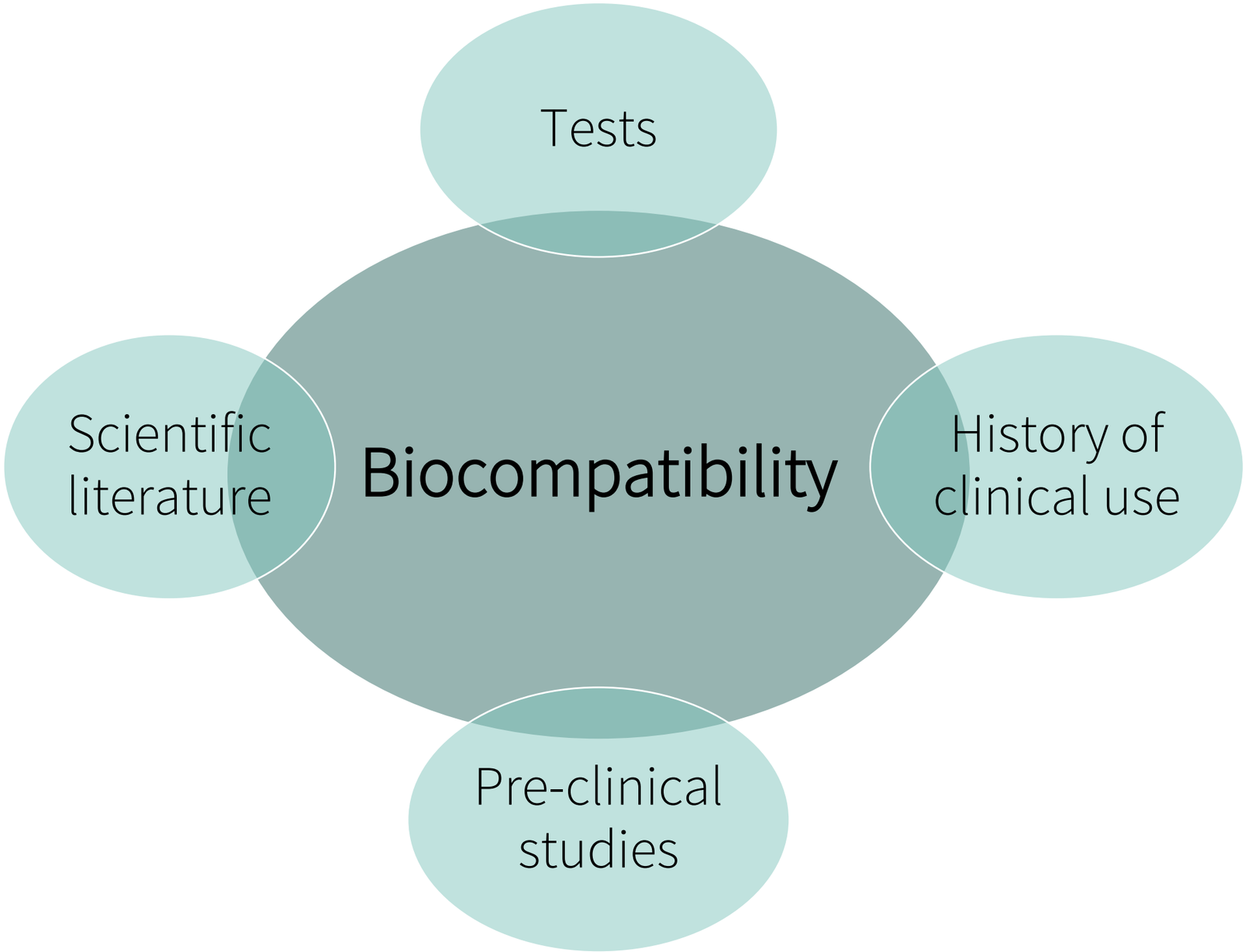
Biocompatibility

The ability of a medical device or material to perform with an appropriate host response in a specific situation.

Due to differences in patient reactions to the same material, it is possible that some patients may have adverse tissue reactions even to well-established biocompatible materials.

[1] Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process”, FDA, September 4, 2020
[2] ISO 10993-1:2018. Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process

How Is Biocompatibility Assessed?



History of Biological Safety Evaluation

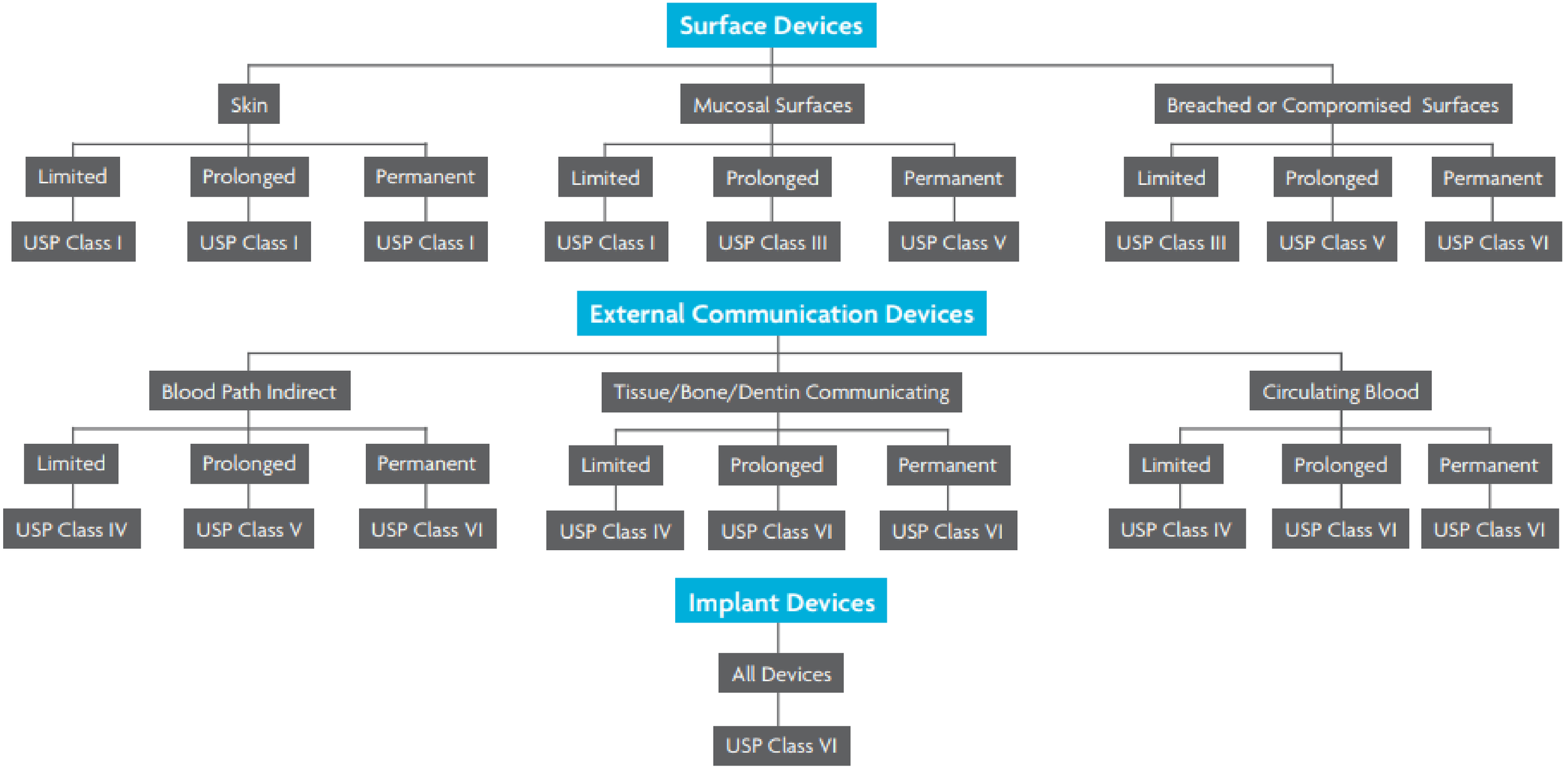
United States Pharmacopoeia (USP)

- 1980's: Use of drug container and pharmaceutical based methods
  - Examination of material chemistry / extractables
  - USP <87> Biological reactivity tests, In Vitro = Cytotoxicity
  - USP <88> Biological reactivity tests, In Vivo = acute systemic toxicity, intracutaneous reactivity, and implantation
  - USP Classes I - VI

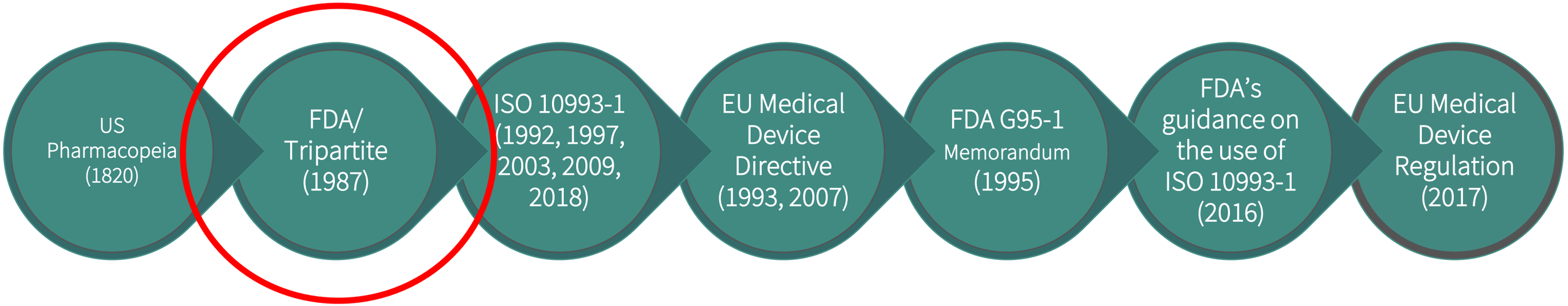
Table 1. Classification of Plastics

Plastic Classes[a]						Tests to be Conducted		
I	II	III	IV	V	VI	Test Material	Animal	Dose
x	x	x	x	x	x	Extract of *Sample* in *Sodium Chloride Injection*	Mouse	50 mL/kg
x	x	x	x	x	x		Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites
	x	x	x	x	x	Extract of *Sample* in *1 in 20 Solution of Alcohol in Sodium Chloride Injection*	Mouse	50 mL/kg
	x	x	x	x	x		Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites
		x		x	x	Extract of *Sample* in *Polyethylene Glycol 400*	Mouse	10 g/kg
				x	x		Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites
		x	x	x	x	Extract of *Sample* in *Vegetable Oil*	Mouse	50 mL/kg
			x	x	x		Rabbit or Guinea Pig	0.2 mL/animal at each of 10 or 6 sites
			x		x	Implant strips of *Sample*	Rabbit	4 strips/animal
			x		x	Implant *Sample*	Rat	2 *Samples*/animal

USP Plastics Designations



FDA/Tripartite Biocompatibility Guidance G87-1



FDA/Tripartite Biocompatibility Guidance G87-1

- FDA released General Program Memorandum G87-1 Tripartite Biocompatibility Guidance – April 24, 1987
- Common approach for evaluating toxicity of medical devices
- Provided framework for application of 7 principles for toxicity evaluation
- Formally introduced device categories based on nature and duration of contact
- Introduction of additional biological tests/effects

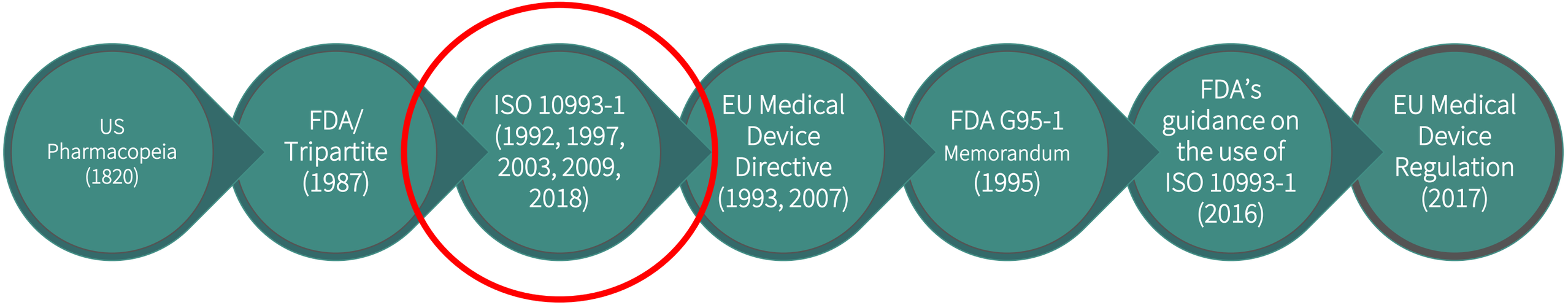
Device Categorization (G87-1)

- Non-Contacting Devices
- External Devices
  - Intact Skin
  - Breach or Compromised Surfaces
- Externally Communicating Devices
  - Intact Natural Channels
  - Blood Path, Indirect
  - Blood Path, Direct
- Internal/Implant Devices
  - Bone
  - Tissue and Tissue Fluid
  - Blood

Intended Use vs. Risk

Brain	30+ days (long-term)
Urinary tract	5 min to 29 days (short-term)
Skin	<5 min (transient)

International Standardization



The 1990s and Beyond: Standardization through ISO

ISO 10993:
Biological Evaluation of Medical Devices

ISO 10993-1: Biological Evaluation of Medical Devices

- 1992 – Guidance on selection of tests
- 1997, 2003 – Evaluation and testing
- 2009 – Evaluating and testing with a Risk Management Process
  - The term “risk” appears for the first time
  - Risk-based vs. test-based
- 2018 – Extended and more detailed (especially physical and chemical characterization)

ISO 10993-1: Biological Evaluation of Medical Devices

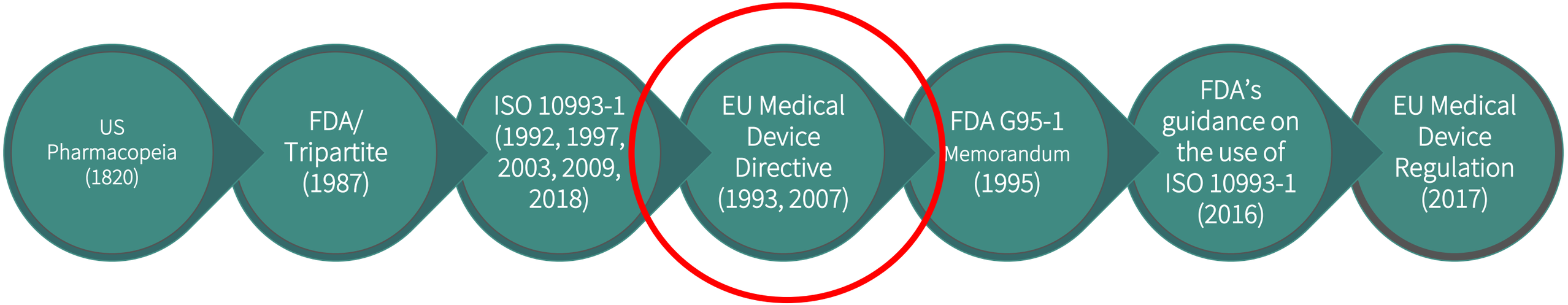
Primary aim: "… the protection of humans from potential biological risks arising from the use of medical devices."

Scope: "… the assessment of the biological safety of the medical device."

Biological risk: *"combination of the probability of harm to health occurring as a result of adverse reactions associated with medical device … or material … interactions, and the severity of that harm"*

Biological safety: *"freedom from unacceptable biological risk … in the context of the intended use"*

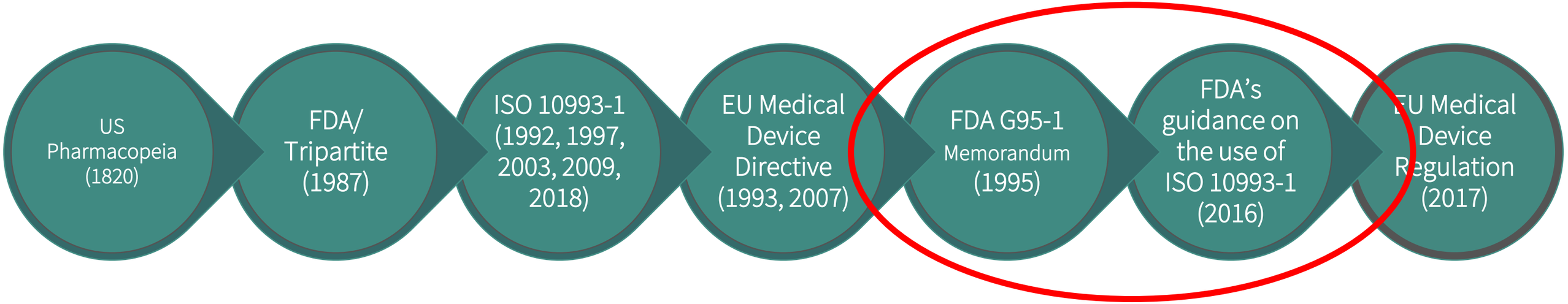
European Union Guidance



EU Medical Device Directive

- Particular attention must be paid to:
  - Choice of materials, with regards to toxicity
  - Compatibility between the materials and biological tissues, cells, and bodily fluids, accounting for intended purpose
- Minimize risk posed by contaminants and residues, with attention to type of tissue, as well as duration and frequency of exposure
- Specific mention of carcinogenic, mutagenic or toxic to reproduction substances

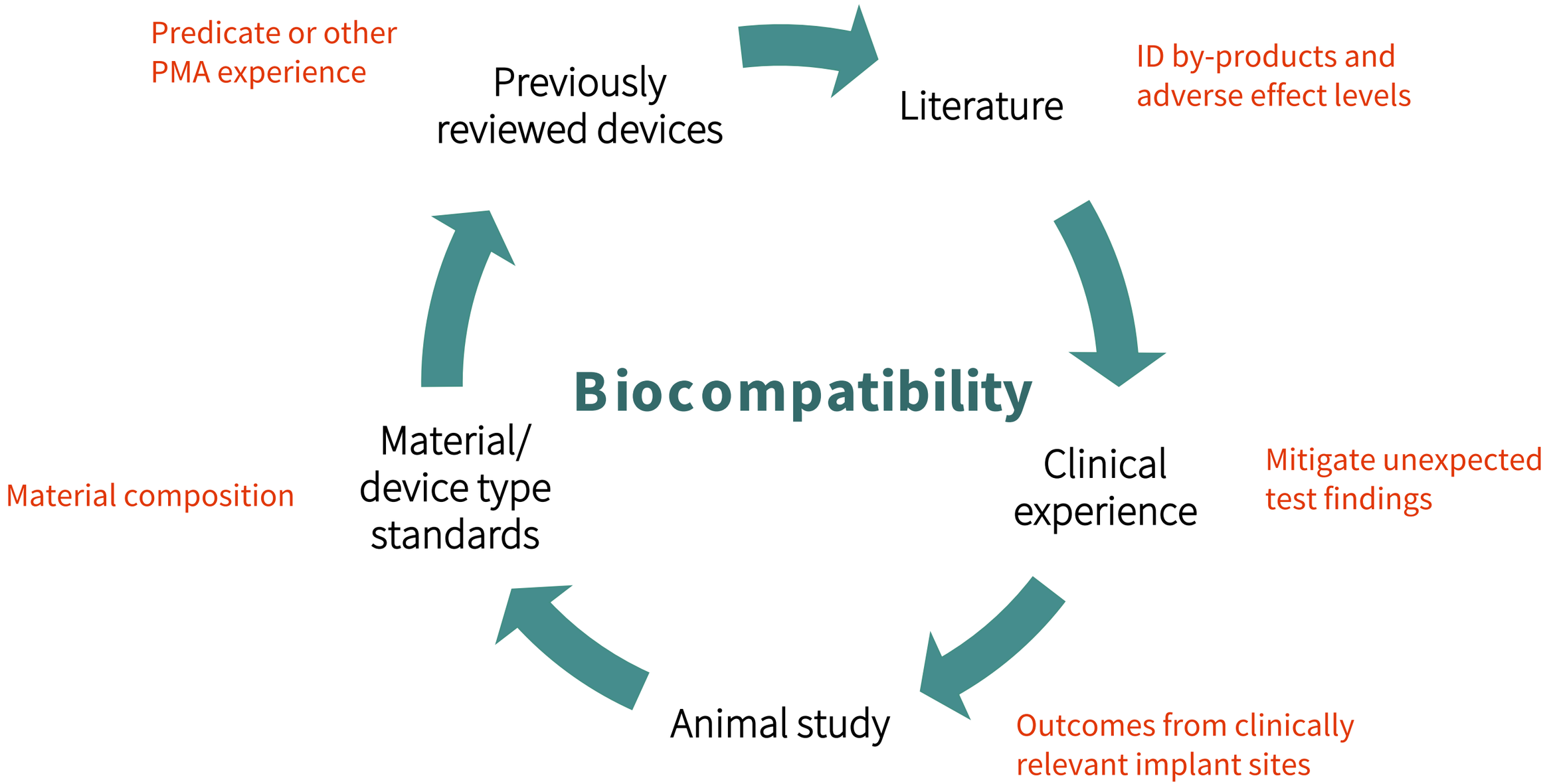
FDA Guidance



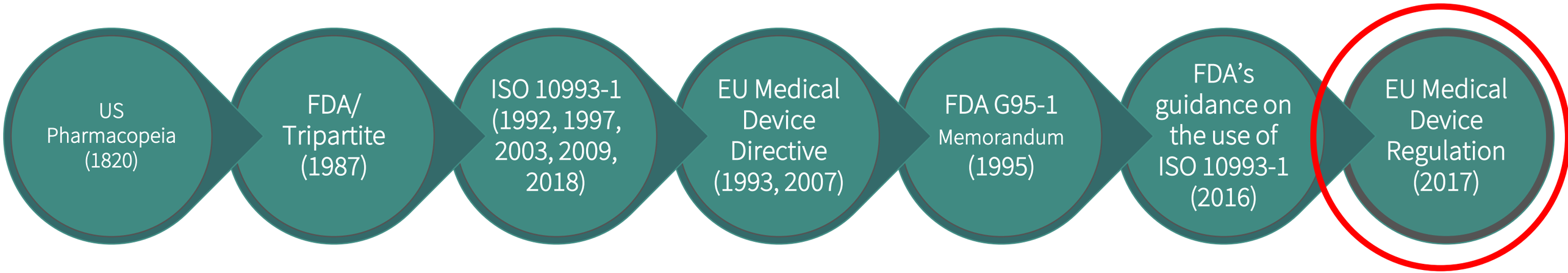
FDA Guidance

- 1995: Blue Book Memorandum #G95-1
  - Replaced the G87-1 Memorandum
  - FDA's recognition and description of use of ISO 10993-1:1992
  - Introduced FDA's modified tables, including consideration for additional tests
- 2016-2020: New Biocompatibility Guidance
  - Replaced the G95-1 Memorandum
  - Expanded on ISO 10993-1:2009, particularly if novel materials or manufacturing processes are used
  - Specific endpoint considerations and recommendations for sample preparation
  - Considerations for hazards from mechanical failure
  - Use of risk-based approaches to determine if testing is needed

FDA Guidance: Sources for Risk Assessment



EU Regulations



EU Medical Device Regulation

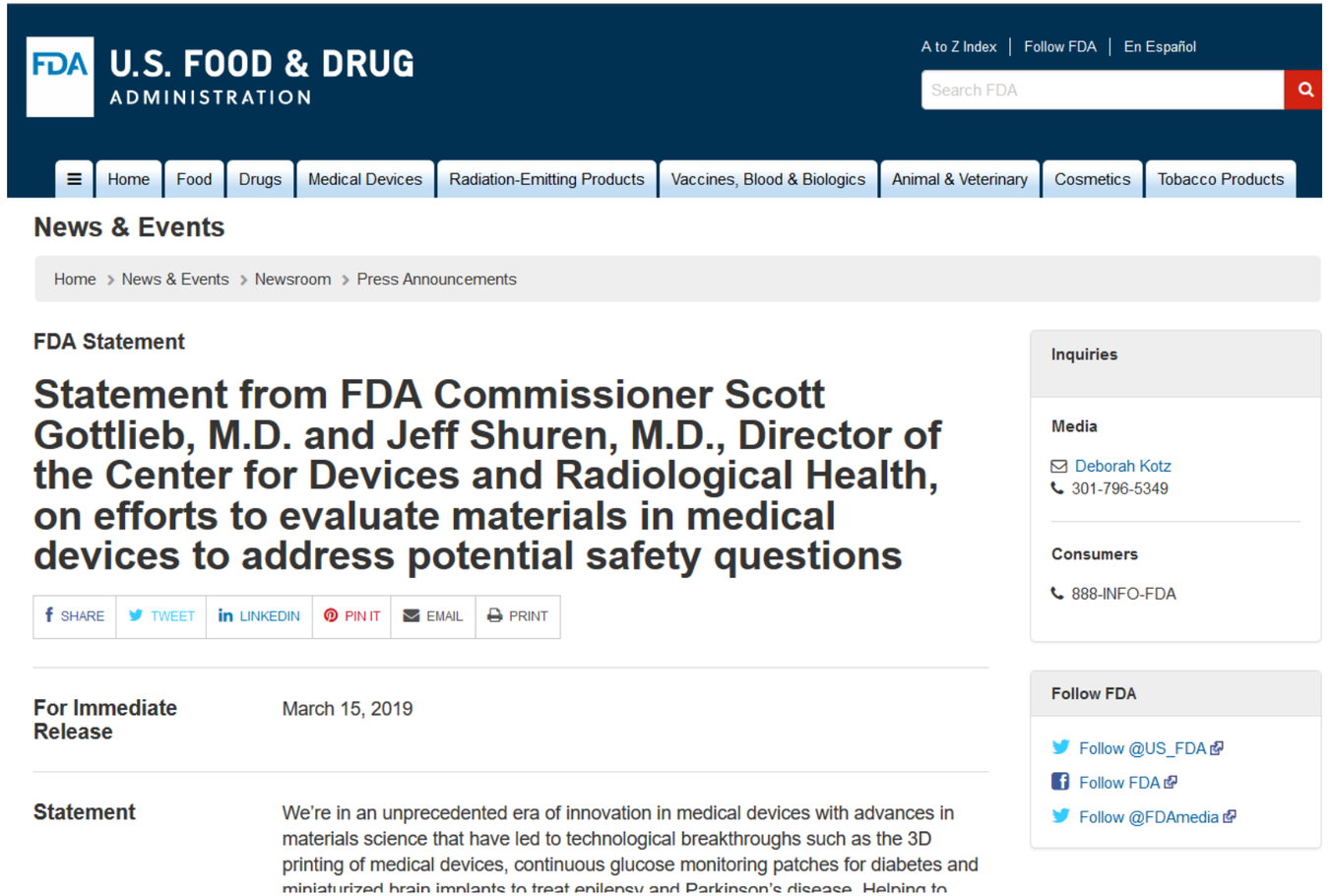
- Compliance with ISO 10993
- Added requirements for:
  - Concentration thresholds of certain substances, unless justified
  - Devices incorporating non-viable human tissues or cells
- Considerations for endocrine-disrupting substances, nanomaterials, and devices composed of absorbed or locally dispersed in the body

FDA and Medical Device Materials

Medical Device Materials

- Concerns about small number of patients may have biological responses to certain types of materials in implantable or insertable devices
- Symptoms may be limited to region where the device is implanted, may not develop for several years following implantation, or may be limited to small subsets of patients
- Enhancing materials science understanding may lead to “identifying materials that may cause an exaggerated response in sensitive individuals and advance the development of safer materials”
- Finalized updated biocompatibility guidance to clarify expectations in 2016

March 15, 2019



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FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D. and Jeff Shuren, M.D., Director of the Center for Devices and Radiological Health, on efforts to evaluate materials in medical devices to address potential safety questions

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For Immediate Release March 15, 2019

Statement We’re in an unprecedented era of innovation in medical devices with advances in materials science that have led to technological breakthroughs such as the 3D printing of medical devices, continuous glucose monitoring patches for diabetes and miniaturized brain implants to treat epilepsy and Parkinson’s disease. Helping to

Inquiries

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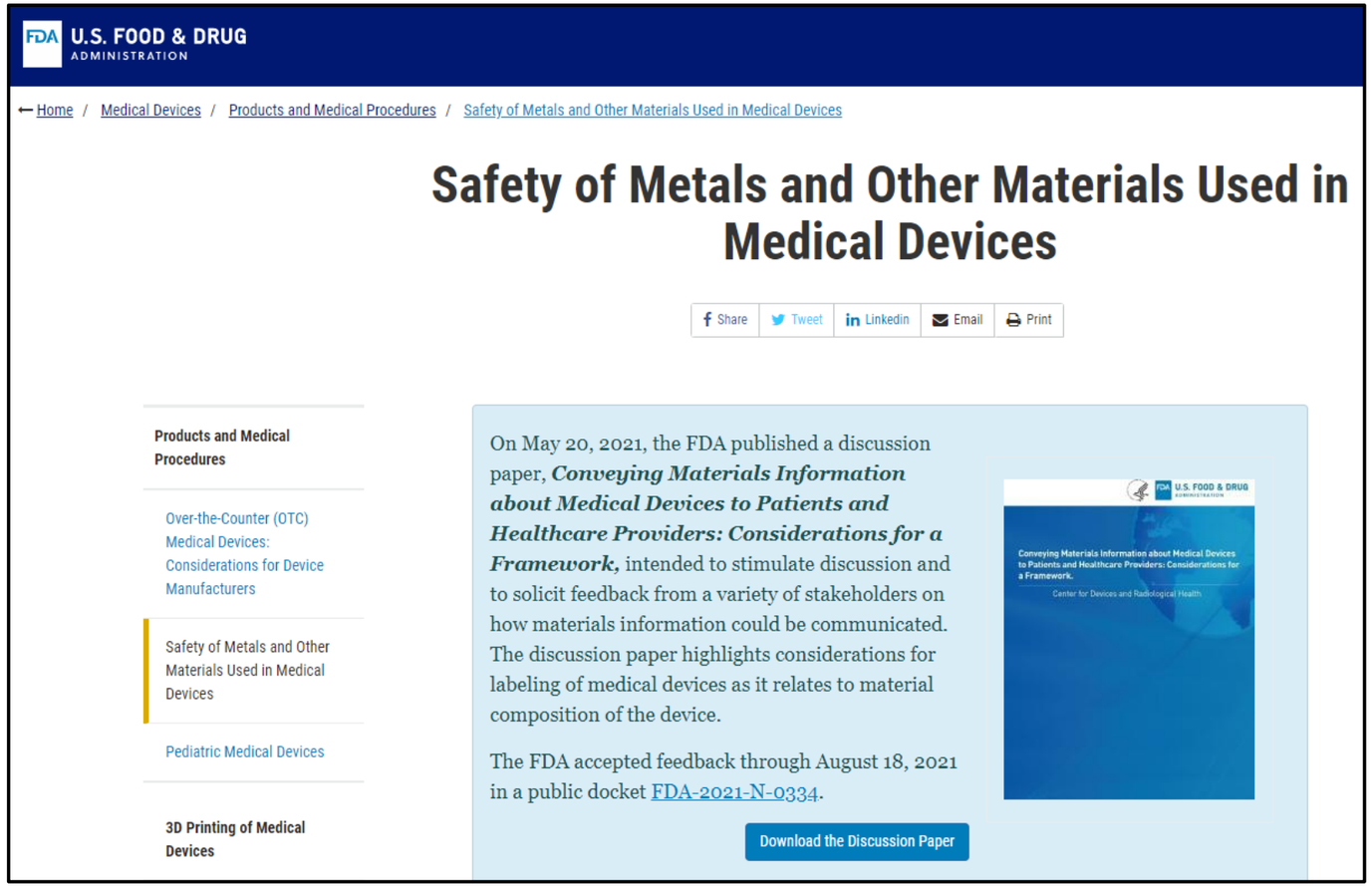
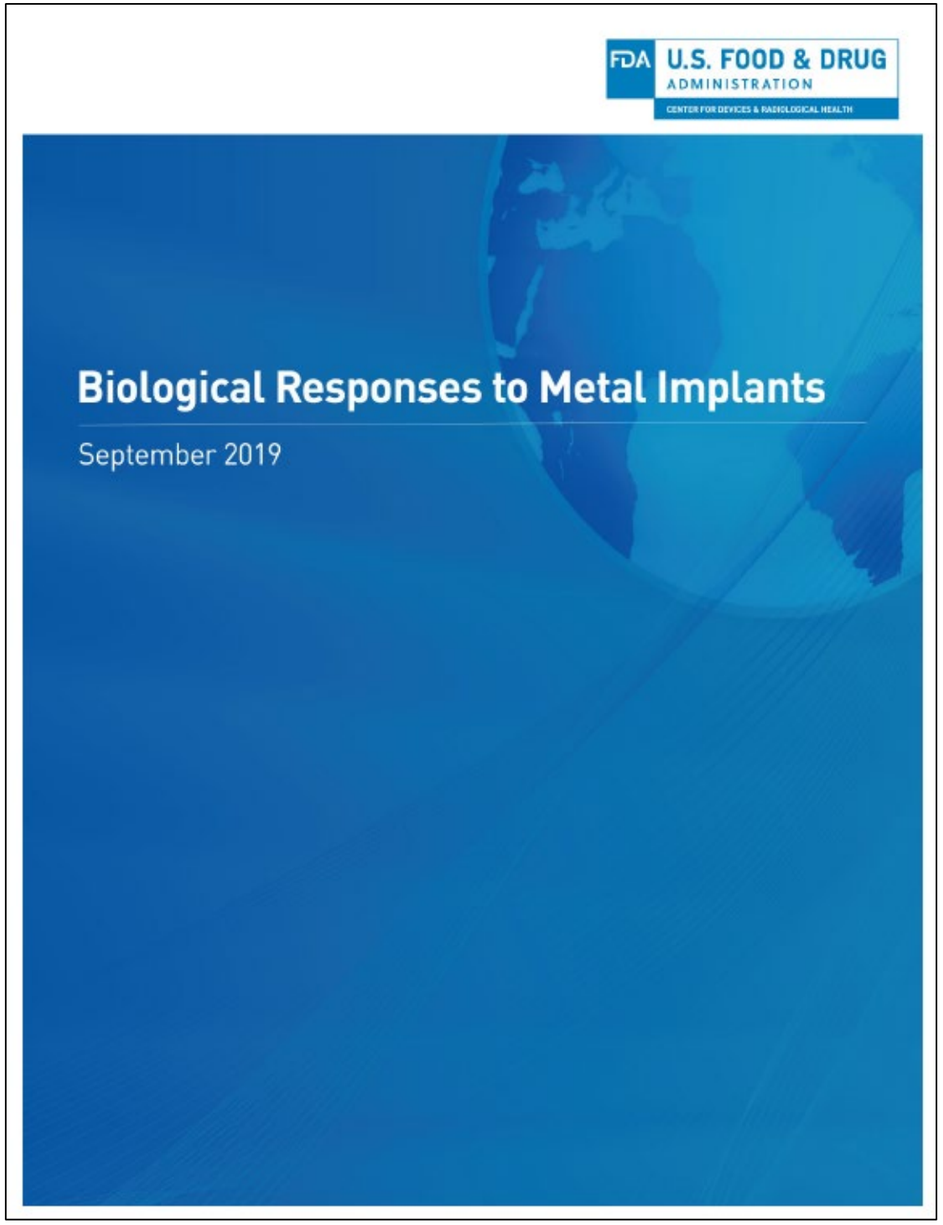
Medical Device Materials

- Described to stakeholders how FDA considers the safety of materials in medical devices
- FDA's role in postmarket review of data associated with certain metal-containing implants
- FDA's issuance of paper on biological responses to metal implants
- FDA has initiated research efforts on knowledge gaps re: immunological responses



Biological Responses to Metal Implants

- How a patient's immune system may respond to metal and does response produce clinically significant signs, symptoms or adverse outcomes?



Biological Responses to Metal Implants

- Corrosion and metal ion release
  - Physiological environment
  - Mechanical interactions
  - Active implants – electrical stimulation
  - Processing, e.g., surface finish
- Orthopedic devices
  - Bone loss
- Neurologic devices (electrodes, nitinol coils)
  - Effects on electrical signals from brain
  - Nickel ion liberation
- Cardiovascular devices
  - Thrombus formation
  - Coatings to facilitate responses
- Oral/dental implants
  - Role of bacterial and fungal microbes
- Urogenital devices
  - Copper ions and microbial biofilms in intrauterine devices

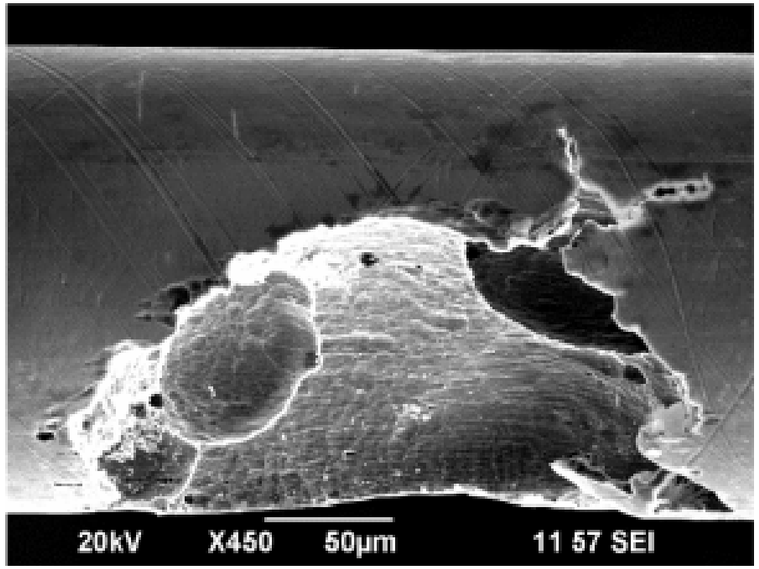


Figure 1: Example of pitting corrosion on the surface of stainless steel (Di Prima, Guiterrez, and Weaver 2017).[6]

Biological Responses to Metal Implants

7 CLINICAL RESPONSE TO METAL IMPLANTS

The clinical response to metal implants is complicated and no simple explanation for the wide variety of reported adverse responses is available. Despite commonly used terms such as "metal allergy" or "metal hypersensitivity", current published evidence suggests that allergic mechanisms alone do not explain most responses to metal implants. Harmful responses, when they do occur, are likely the result of device, biomaterial, and patient-related factors. Individual patient susceptibility plays an important role in the outcome.

Recent issues with metal-on-metal orthopedic implants and gynecological metal implants highlighted concerns about the potential safety of certain types of metal implants. A broad spectrum of clinical responses have been reported and often more than one response can arise in the same patient. The entire spectrum of local and systemic findings related to metal implants is incorporated into the term "adverse reaction to metal debris" (ARMD). More frequent ARMDs include local responses such as pain, skin rash, tissue destruction including bone loss (osteolysis), escape of fluid from the joint (joint effusion), and solid and cystic masses called pseudotumors. Systemic responses such as depression, hearing loss, vertigo (dizziness), and neurologic and cardiac damage have also been reported by patients that have metal implants, although the determination of whether the metal caused the event(s) is often not possible.

Standard tests, such as metal ion levels in the blood stream or skin patch tests for metal allergies, correlate poorly with adverse responses. In some cases, patients with adverse diagnostic findings present no symptoms. For this reason, management of patients with metal implants is divided into proactive monitoring for asymptomatic patients and more aggressive diagnostic and therapeutic approaches for patients with clinical symptoms.

Clinical response is complicated and no simple explanation

Individual patient susceptibility plays an important role

Determination of whether the metal caused the systemic response is often not possible

Biological Responses to Metal Implants

- "… the mechanisms underlying the biological responses to metal implants are not fully understood. Because of this, it is difficult to distinguish between the device- and patient-related factors in addressing safety and effectiveness concerns."
- "Because metal corrosion testing is typically done under idealized conditions, which enables comparisons between devices, it is still unclear how *in vitro* engineering performance correlates to the corrosion behavior with *in vivo* implantation."
- "Limitations in biocompatibility assessments thus present unique challenges in premarket evaluation of the device."

Material Safety

- "… we have partnered with ECRI to study and publish safety profiles for materials that are commonly used in implantable medical devices and the effects of those materials on patients over time. These evaluations are part of the FDA's broader initiative to improve the safety of medical devices through the use of safer materials and preventing patients at risk for an adverse response to select materials from receiving devices that contain them."

Sep 22, 2021


FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA IN BRIEF

FDA In Brief: FDA Publishes Material Safety Data to Promote Safer, More Effective Medical Devices

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For Immediate Release: September 22, 2021

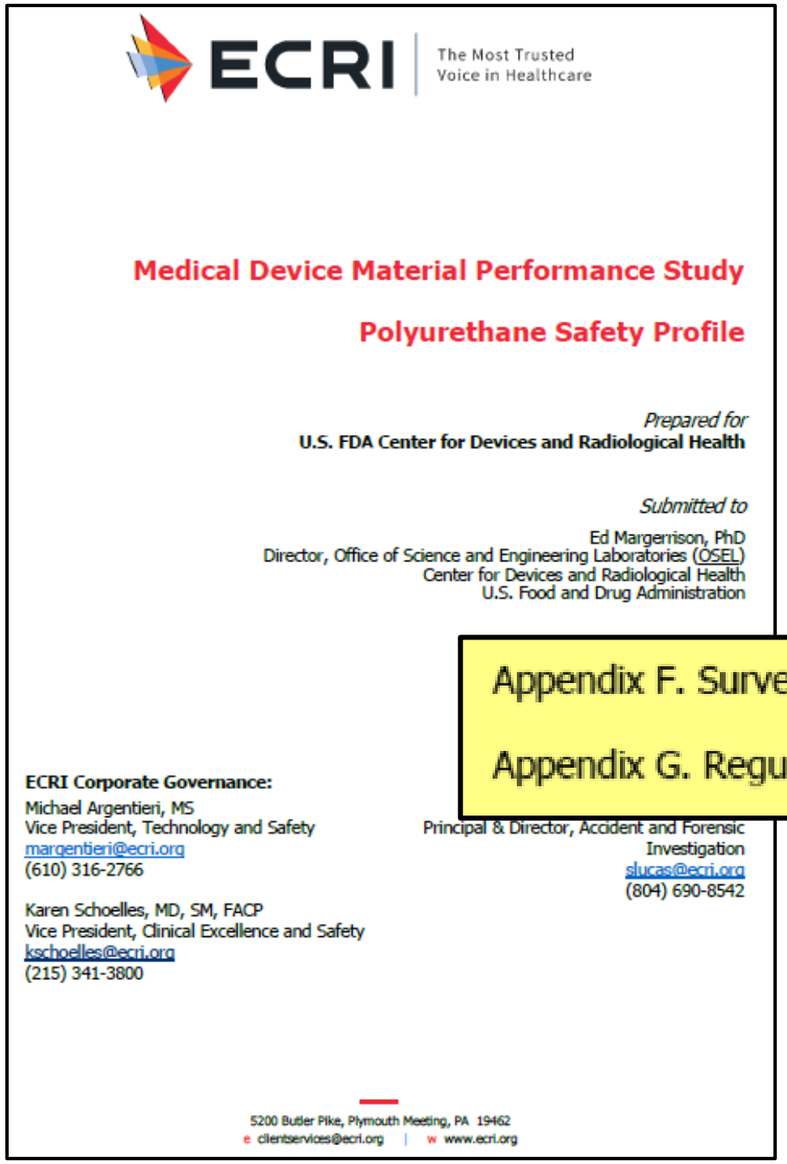
Material Safety

- Magnesium
- Polypropylene (e.g., in surgical mesh)
- Polyurethanes
- Siloxanes (e.g., in breast implants)
- PET (polyethylene terephthalate)
- PEG (polyethylene glycol) (e.g., as stent and catheter coatings)
- Silver (e.g. as antimicrobial agent)
- Acrylic acid derivatives (e.g., in dental resins)
- Polyhydroxy acids (PLA, PGA, etc.) (e.g., as bioresorbable polymers)

Material Safety

- What is the typical or expected local host response to the material?
- Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
- Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
- Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
- What critical information gaps exist and what research is needed to better understand this issue?

ECRI Report: Polyurethane



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Medical Device Material Performance Study

Polyurethane Safety Profile

Prepared for
U.S. FDA Center for Devices and Radiological Health

Submitted to
Ed Margerrison, PhD
Director, Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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ECRI Report: Polyurethane

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ECRI Report: Polyurethane Executive Summary

- 82 articles included in review
- Local responses: Mild inflammation, catheter dysfunction, phlebitis, and thrombosis (moderate evidence)
- Unclear whether device malfunctions related to biocompatibility or device integrity
- No studies investigated systemic reactions
- Most common complication in ECRI data was related to “device malfunction or failure”
- Evidence gaps with patient or material related factors for local responses

Summary

- Biocompatibility relates to the ability of a device material to perform with an appropriate host response based on the specific situation. Some patients may still experience adverse tissue reactions, even to well-established biocompatible materials.
- Potential biocompatibility risks are assessed using a risk management process. This does not always necessitate testing, particularly when applicable prior data or experience exists.

Summary

- Biological evaluation should be taken in the benefit-risk perspective.
- Biocompatibility is only one of a number of design characteristics; selecting a material based solely on its biocompatibility might result in a less functional device.

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