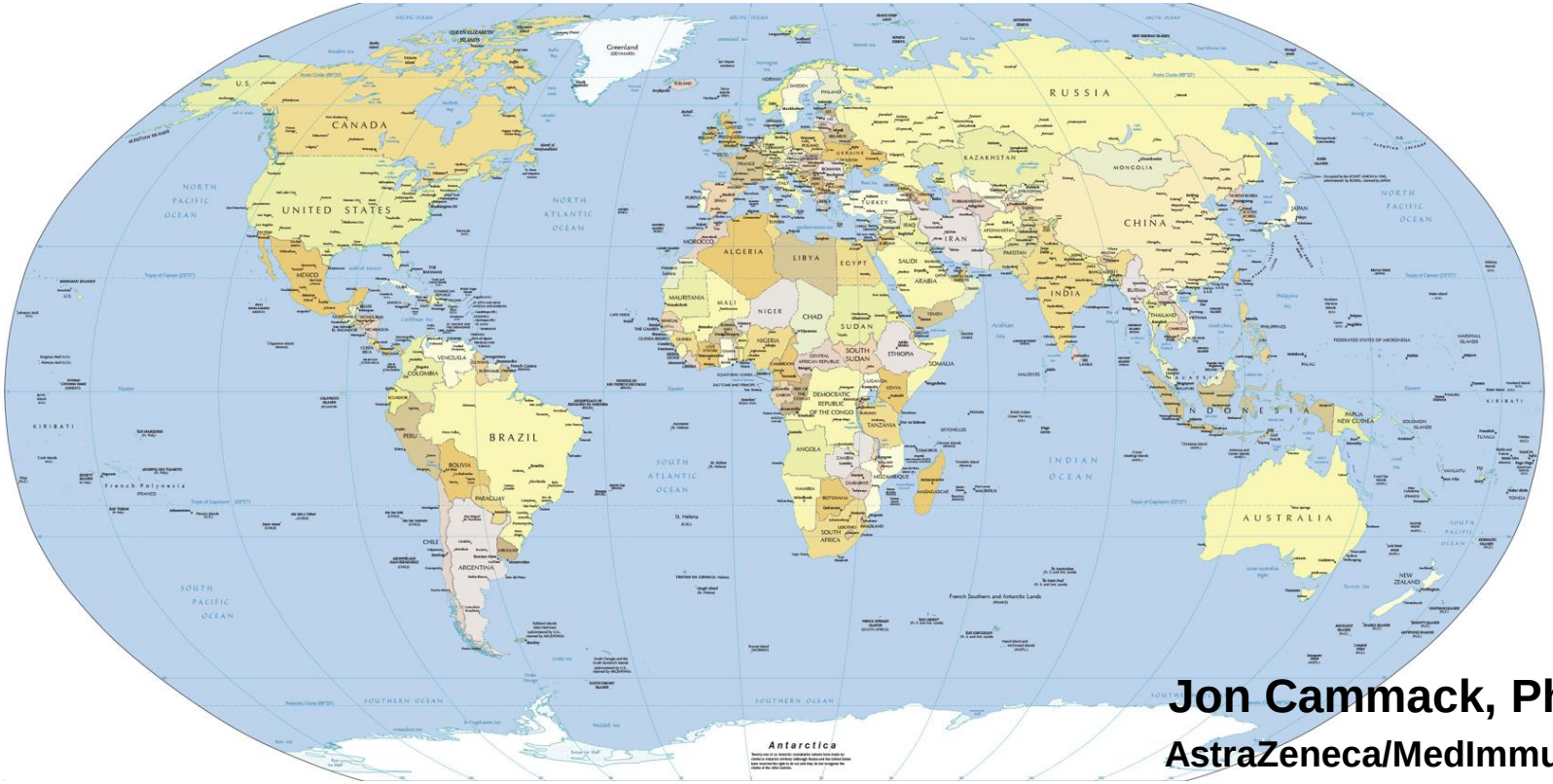
# Medical Device Biocompatibility:

## ISO TC194 Overview & 10993 Standards

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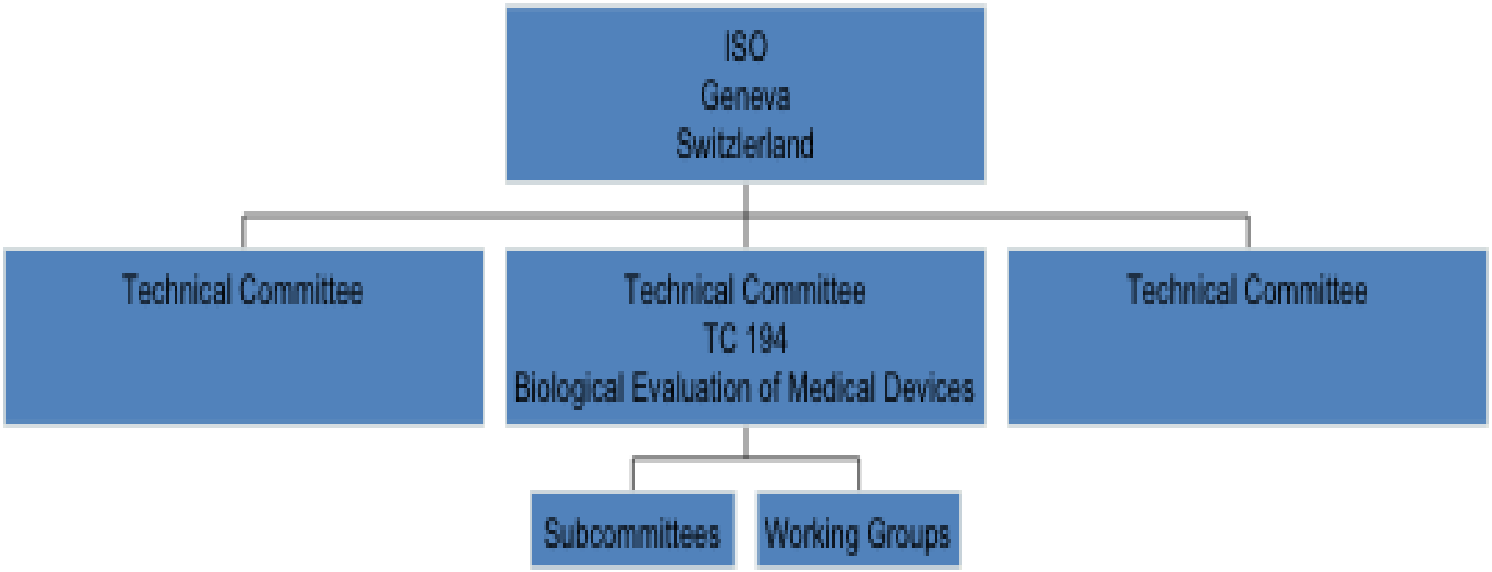
# Overview

- ISO TC194 Structure, Function
- Background & History
- ISO TC194 Current Standards
- Risk Management Evolution

# ISO Structure/Function



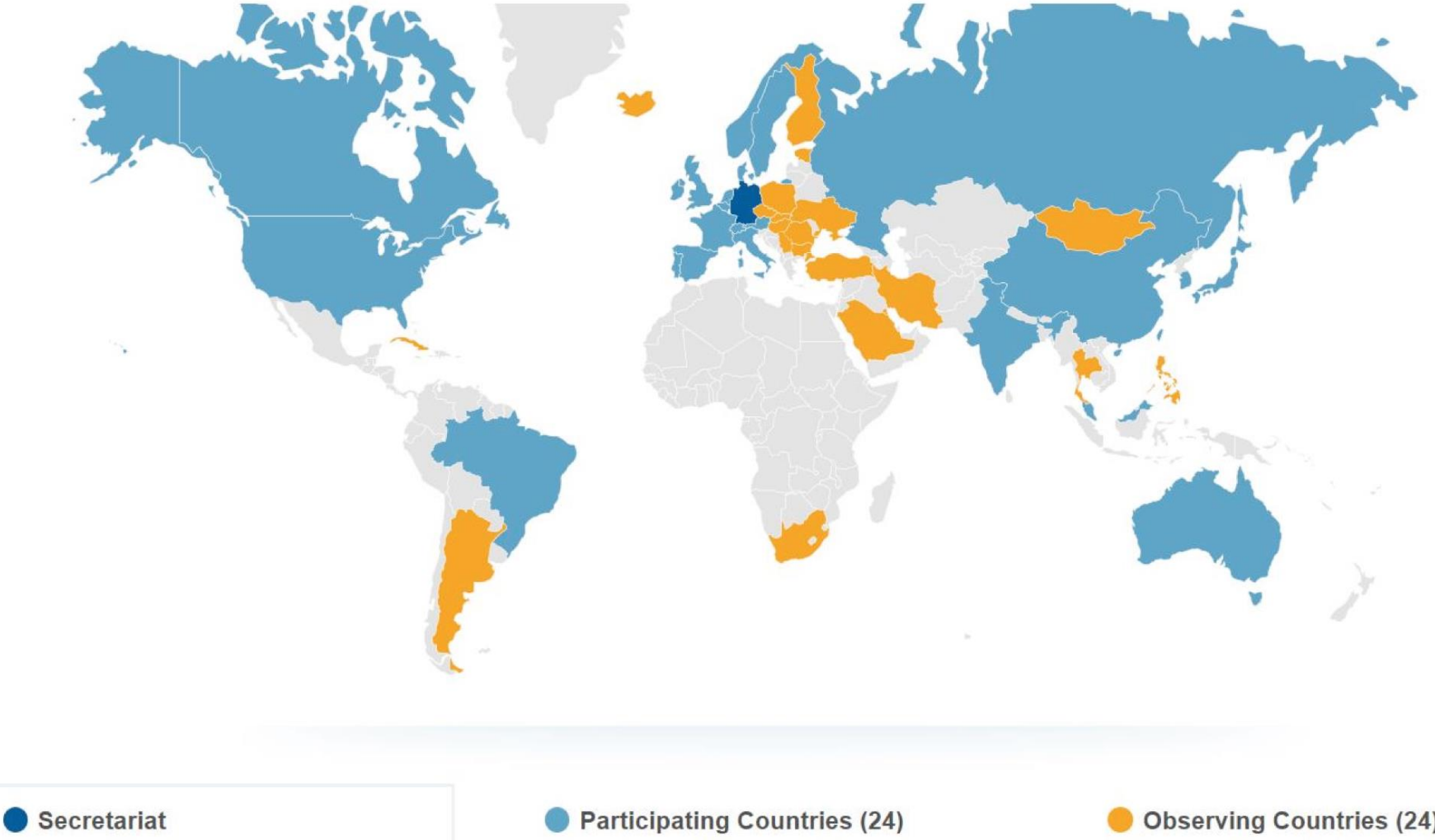

- 162 member countries – the national standards bodies worldwide
- Nearly 300 Technical Committees within ISO
- In the US, the National Standards body is ANSI
- AAMI is the ANSI delegated organization that develops and publishes TC194 Stds
- ISO TC194 Stds are the ISO 10993 series

# Mission of ISO TC194

*TC 194 will contribute indirectly to public health and well-being by developing standards for medical devices - conformity to the standards by manufacturers will ensure their products do not compromise the biological and clinical safety of patients through:*

- **Protection of the health and safety of the patient and user**
- **Elimination of trade barriers through global harmonization**
- **Uniformity of test methods**
- **Uniformity of reference materials**
- **Uniformity of terminology and definitions**
- **Quality products used in medical devices**
- **Effective and efficient use of resources in standards development**

# ISO TC194 Countries



# ISO TC194/10993 Standards Background & History

## Medical Device Safety Assessment Evolution


**1950's**: Compendial (USP, EP, others) tests developed largely for raw material screening purposes

**1986**: TriPartite Agreement developed: US, UK, Canada

**1992**: ISO 10993 Initiated: N. America, Europe, Asia

**1995**: FDA G95 Bluebook memo: "formal" FDA acceptance of ISO 10993

**2010**: ISO 10993 – Risk Management Approach

# Foundation - Tripartite

THE FOLLOWING TABLE LISTS THE BIOLOGICAL TESTS THAT MIGHT BE APPLIED TO EVALUATING THE SAFETY OF MEDICAL DEVICES MADE OF *Polymers*. THIS DOES NOT IMPLY THAT ALL THE TESTS LISTED UNDER EACH CATEGORY WILL BE NECESSARY OR RELEVANT IN ALL CASES. TESTS FOR DEVICES MADE OF METALS, CERAMICS, BIOLOGICAL MATERIALS, ETC. ARE NOT INCLUDED HERE BUT ARE UNDER CONSIDERATION.

CATEGORIZATION OF MEDICAL DEVICES IS BASED ON BODY CONTACT AND CONTACT DURATION.

| *Device categories* | | *Biological tests* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Short-term* | | | | | | | | *Long-term* | | |
| *Body contact* | *Contact Duration*[a] | *Irritation tests* | *Sensitization assay* | *Cytotoxicity* | *Acute systemic toxicity* | *Hemocompatibility/ hemolysis* | *Pyrogenicity (material-mediated)* | *Implantation tests* | *Mutagenicity (Genotoxicity)* | *Subchronic toxicity* | *Chronic toxicity* | *Carcinogenesis bioassay* |
| External devices | | | | | | | | | | | | |
| Intact surface | A | • | • | • | | | | | | | | |
| | B | • | • | • | | | | | | | | |
| | C | • | • | • | • | | | | | | | |
| Breached or compromised surface | A | • | • | • | • | • | | | | | | |
| | B | • | • | • | • | • | | | | • | | |
| | C | • | • | • | • | • | | • | • | • | • | |
| Externally communicating devices | | | | | | | | | | | | |
| Intact natural channels | A | • | • | • | • | • | • | • | | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |
| Blood path indirect | A | • | • | • | • | • | • | • | • | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |
| Blood path direct | A | • | • | • | • | • | • | • | • | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |
| Internal devices | | | | | | | | | | | | |
| Bone | A | • | • | • | • | • | • | • | • | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |
| Tissue and tissue fluids | A | • | • | • | • | • | • | • | • | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |
| Blood | A | • | • | • | • | • | • | • | • | | | |
| | B | • | • | • | • | • | • | • | • | • | | |
| | C | • | • | • | • | • | • | • | • | • | • | • |

(1) For those devices with possible leachables or degradation products, e.g. absorbable sutures, hemostatic agents etc., testing for pharmacokinetics may be required. (2) Reproductive and developmental toxicity tests may be required for certain materials used for specialized indications. (3) Consideration should be given to long-term biological tests where indicated in the table, taking into account the nature and mobility of the ingredients in the materials used to fabricate the device.

[a] A = Transient (< 5 minutes); B = short-term (5 minutes-29 days); C = long-term (≥ 30 days).

# Device Biological Testing: Described in ISO 10993-1

## Materials/devices categorized according to:

- **Body Contact:**
  **Surface devices:** skin, mucosal membranes, breached body surfaces
  **External communicating devices:** blood path-indirect, blood path-circulating, tissue/bone
  **Implant devices:** tissue/bone, blood

- **Duration of Use:**
  **A. Limited:** **< 24 hours**
  **B. Prolonged:** **> 24 hours but < 30 days**
  **C. Permanent:** **> 30 days**

# Categories of Medical Devices & Materials of Construction

*Examples:*

| Surface Device | Externally Communicating | Implant Device |
|---|---|---|
| Gloves | Blood Sets | CSF Shunts |
| Endotracheal Tubes | IV Catheters | Heart Valves |
| Orthodontic Devices / Dental Prostheses | Dental Cements & Dental Filling Materials | Vascular Grafts |

# Standards in ISO TC194

| 5 | Published ISO deliverables Stage 60.60 |
|---|---|
| ISO 10993–1:2009 + Cor 1:2010 | Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process |
| ISO 10993–2:2006 | Biological evaluation of medical devices – Part 2: Animal welfare requirements |
| ISO 10993–3:2003 | Biological evaluation of medical devices – Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity |
| ISO 10993–4:2002 + Amd 1:2006 | Biological evaluation of medical devices – Part 4: Selection of test for interactions with blood |
| ISO 10993–5:2009 | Biological evaluation of medical devices – Part 5: Tests for *in vitro* cytotoxicity |
| ISO 10993–6:2007 | Biological evaluation of medical devices – Part 6: Tests for local effects after implantation |
| ISO 10993–7:2008 + Cor 1:2009 | Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals |
| ISO 10993–9:2009 | Biological evaluation of medical devices – Part 9: Framework for identification and quantification of potential degradation products |
| ISO 10993–10:2010 | Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization |
| ISO 10993–11:2006 | Biological evaluation of medical devices – Part 11: Tests for systemic toxicity |
| ISO 10993–12:2007 | Biological evaluation of medical devices – Part 12: Sample preparation and reference materials |
| ISO 10993–13:2010 | Biological evaluation of medical devices – Part 13: Identification and quantification of degradation products from polymeric medical devices |
| ISO 10993–14:2001 | Biological evaluation of medical devices – Part 14: Identification and quantification of degradation products from ceramics |
| ISO 10993–15:2000 | Biological evaluation of medical devices – Part 15: Identification and quantification of degradation products from metals and alloys |
| ISO 10993–16:2010 | Biological evaluation of medical devices – Part 16: Toxicokinetic study design for degradation products and leachables |
| ISO 10993–17:2002 | Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances |
| ISO 10993-18:2005 | Biological evaluation of medical devices – Part 18: Chemical characterisation of materials |
| ISO/TS 10993-19:2006 | Biological evaluation of medical devices – Part 19: Physico-chemical, morphological and topographical characterization of materials |
| ISO/TS 10993-20:2006 | Biological evaluation of medical devices – Part 20: Principles and methods for immunotoxicology testing of medical devices |

# Standards in ISO TC194

| | |
|---|---|
| **6** | **Draft International Standards (ISO/DIS) Stage 40.60** |
| ISO/DIS 10993-6 (Revision) | Biological evaluation of medical devices – Part 6: Tests for local effects after implantation |
| **7** | **Committee Draft (ISO/CD) Stage 30.60** |
| ISO 10993-4.2 (Revision) | Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood |
| ISO/CD 10993-5 (Revision) | Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity |
| **8** | **Approved Work Items (ISO/AWI) Stage 20.00** |
| ISO/AWI 10993-7 | Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals |
| ISO/AWI TS 29741 | Biological evaluation of medical devices -- Development of tolerable intake values for Di(2-ethylhexyl)phthalate (DEHP) |
| **9** | **New projects approved (ISO/NP) Stage 10.99** |
| ISO/NP 10993-1 | Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process |
| ISO/NP 10993-9 | Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products |
| ISO/NP 10993-11 | Biological evaluation of medical devices -- Part 11: Tests for systemic toxicity |
| ISO/NP 10993-15 | Biological evaluation of medical devices -- Part 15: Identification and quantification of degradation products from metals and alloys |
| ISO/NP 10993-16 | Biological evaluation of medical devices -- Part 16: Toxicokinetic study design for degradation products and leachables |
| ISO/NP 10993-18 | Biological evaluation of medical devices -- Part 18: Chemical characterization of materials |
| ISO/NP TS 10993-19 | Biological evaluation of medical devices -- Part 19: Physico-chemical, morphological and topographical characterization of materials |
| ISO/NP TS 10993-20 | Biological evaluation of medical devices -- Part 20: Principles and methods for immunotoxicology testing of medical devices |
| ISO/NP TR 10993-22 | Biological evaluation of medical devices - Part 22: Guidance on nanomaterials |
| **10** | **Preliminary Work Items (ISO/PWI) Stage 00.00** |
| ISO/PWI 10993-17 | Biological evaluation of medical devices -- Part 17: Establishment of allowable limits for leachable substances |

# Current - ISO 10993 Part 1

## Evaluation within a *risk management* process

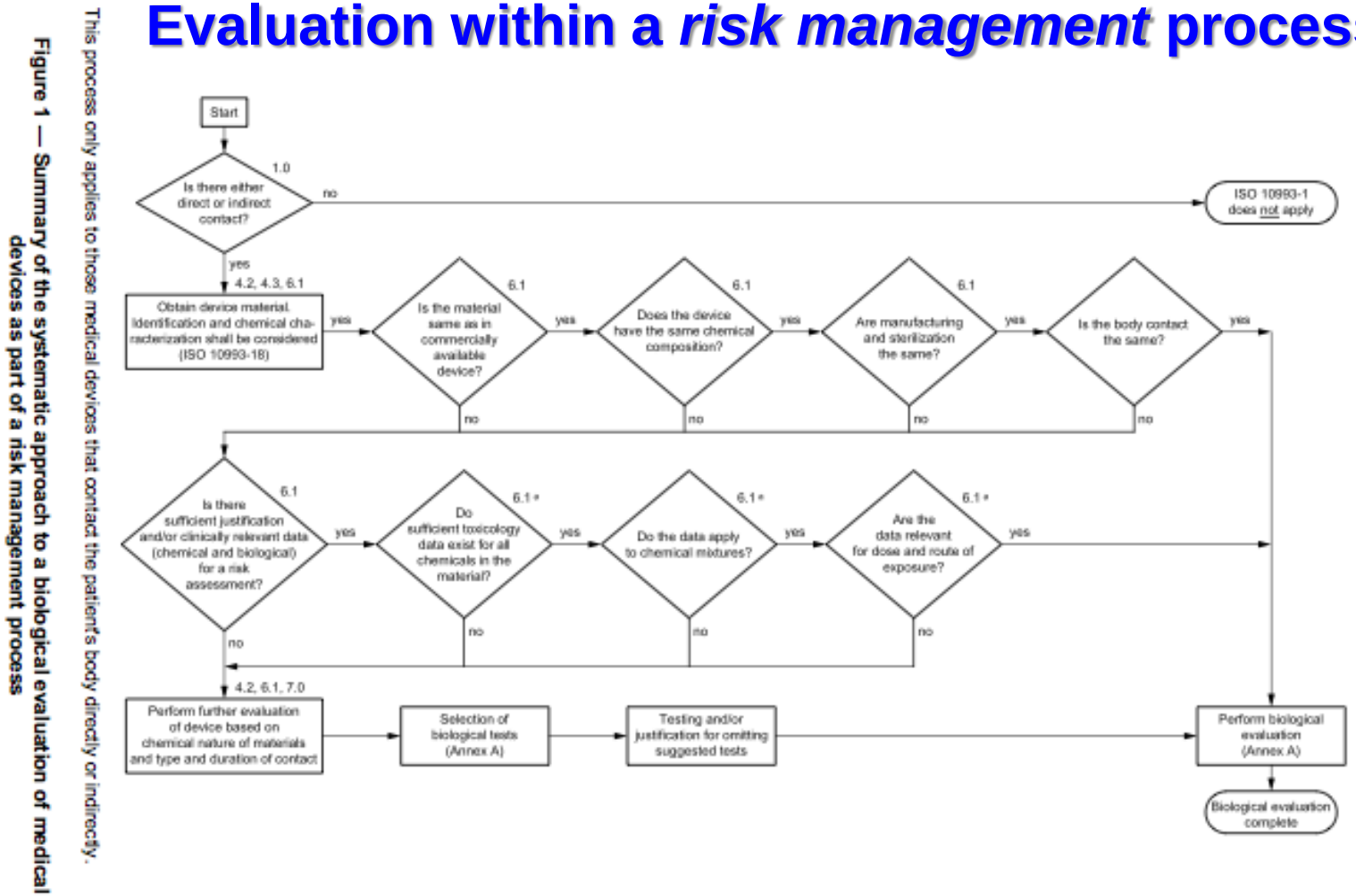
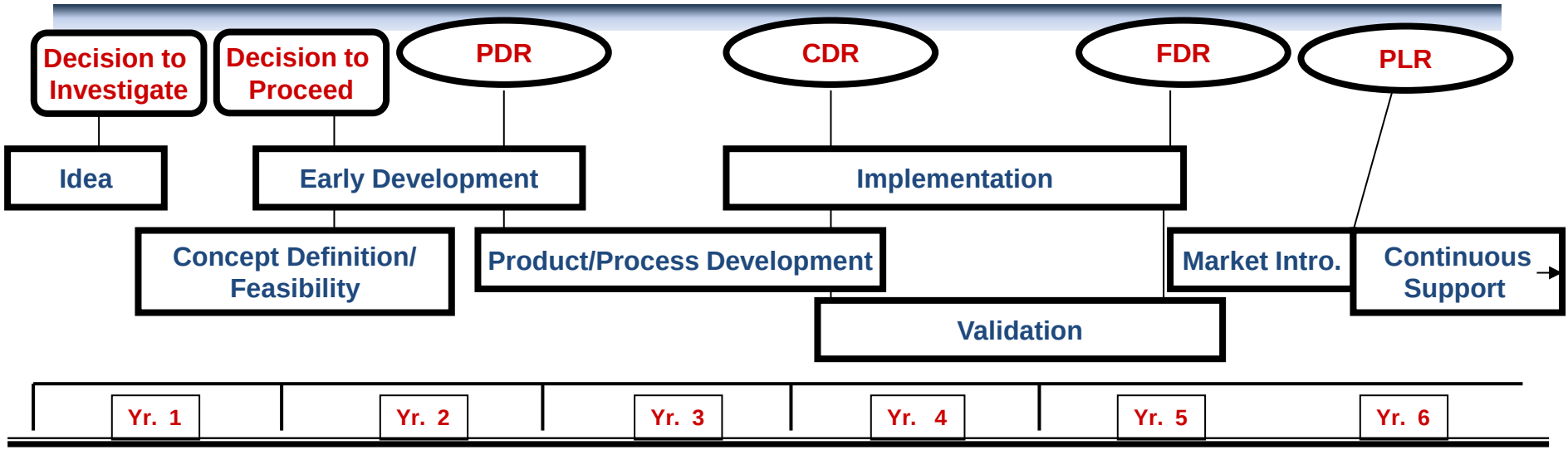



**Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process**

# Risk Management Evolution: Regulatory Environment




- Market and Technical Assessment
- Operating Plan

- Project Team
- Requirements Definition/Design Inputs
- Design Options
- Environmental Assessment
- Preliminary Design Review (s)

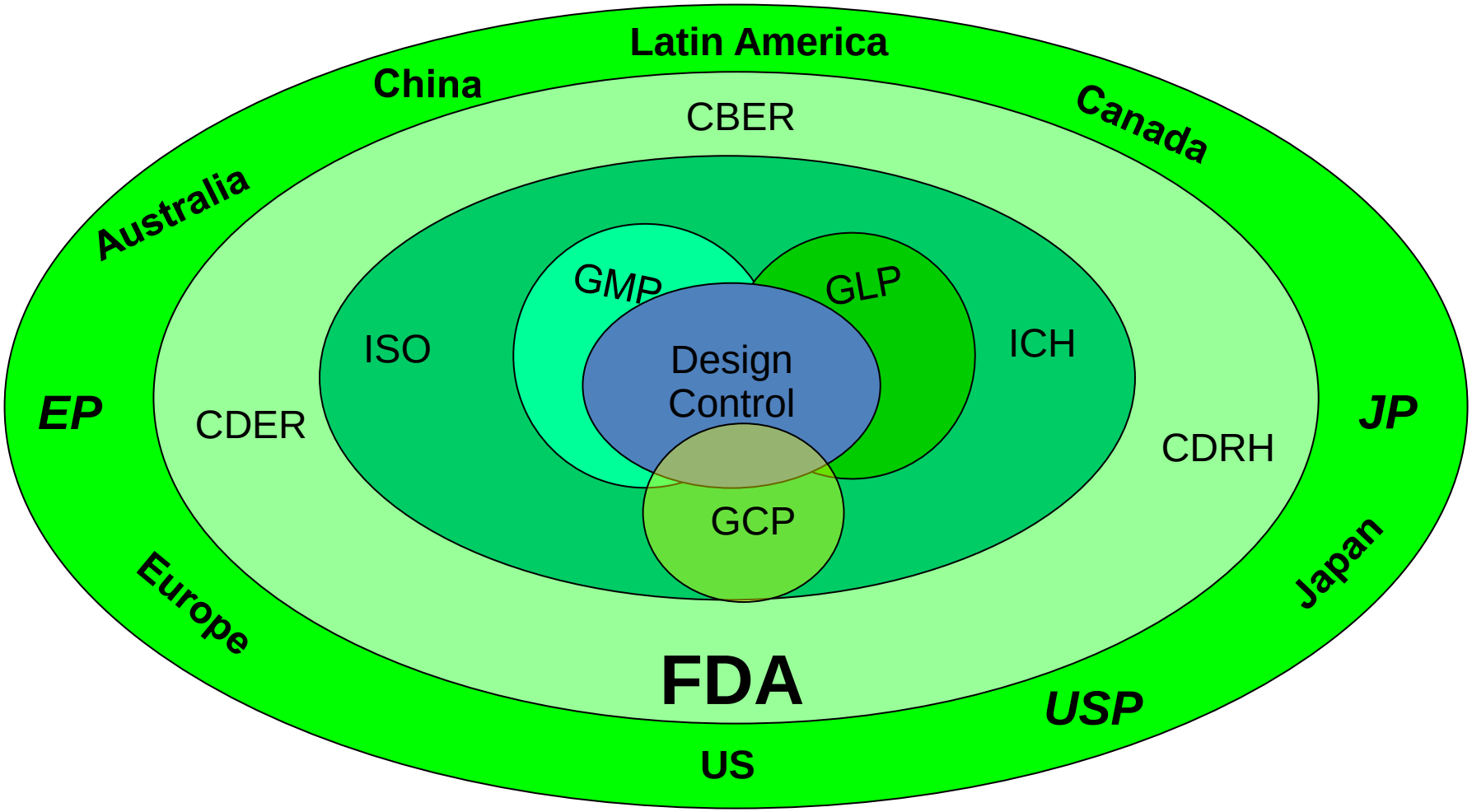
- Product/Process Verification
- Regulatory Plan
- Shelf Life Studies
- PMA/510(k) Submission
- Design Review(s)
- Clinical Appropriateness Review

- Product/Process Validation
- Final Design Review(s)
- Supplier Approval
- Manufacturing Specifications
- Clinical Appropriateness Review
- PMA/510(k) Clearance

- Field Quality Monitoring
- Plant Quality Feedback
- Key Project Lessons Learned

PDR - Preliminary Decision Review
CDR - Critical Decision Review
FDR - Final Decision Review
PLR - Post Launch Review

# Risk Management Evolution: Regulatory Environment



# Risk Management Evolution: Challenges

- Device biocompatibility evaluation is complex!
  - Constantly shifting regulatory environment
  - Chemical *and physical* hazards to consider
    - Assessment of risks from material-tissue interactions, debris, etc.
    - Assessment of risks from leachable chemicals and mixtures
- Device biocompatibility experts as risk managers
  - What does risk management mean?
  - How can we be risk managers?
    - Helping to reduce adverse events needs to be considered

# Risk Management Evolution: Progress & Answers

- Better tools & communication options
  - FDA and other agencies more open to early/often communication
  - Evolving assessment methods
    - E.g., chemical characterization (ISO 10993-18) and risk assessment (ISO 10993-17)
  - Better analytical methods for physical interactions
    - E.g., new imaging tools
- Risk management
  - Adverse event and recall tracking
  - Emerging options for more “holistic” risk management

# Risk Management Evolution: Evolving Tools: Ex 10993-17

**Annex B**
(informative)

**Risk assessment for mixtures of leachable substances**

If the compounds being leached from a device exert their effects via a common toxicological mechanism of action or are structurally similar to one another (e.g., phthalate esters, acrylates, methacrylates), and the dose of these compounds received by a patient is well below the respective TI value for each compound, it can be assumed that any effects will occur in an additive fashion; that is, the combined effects of two or more agents is equal to the sum of the effects of each agent given alone. As a result, a hazard index (HI) approach can be used to estimate the likelihood that adverse effects will occur following exposure to the mixture. An HI can be calculated as follows:

$$HI = \sum_{i=1}^{n} \frac{dose_i}{TI_i} \qquad (B.1)$$

where

$n$ is the number of components of the mixture;

$dose_i$ is the dose of each compound received by the patient, in milligrams per day;

$TI_i$ is the tolerable intake, in milligrams per day, of each compound.

# Risk Management Evolution: Evolving Tools: Ex 10993-17

## *Tolerable Intake (TI)*

**TI** = NOEL, LOEL, or other endpoint
Modifying Factor (MF)

MF = UF1 x UF2 x UF3

**UF1:** inter-individual differences
**UF2:** inter-species differences
**UF3:** quality/relevance of database

Then, **tolerable exposure (TE)**:

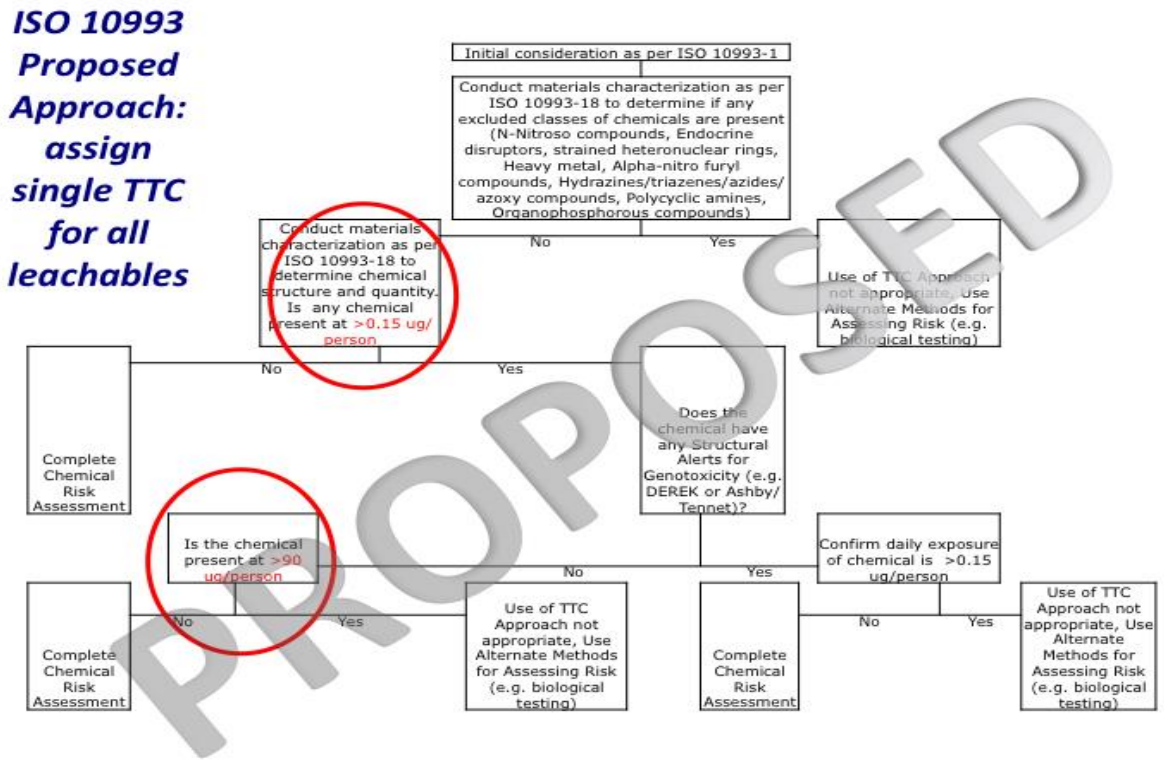
**TE** = TI x *m* x UTF  *m* = body mass; UTF = device utilization factor

Finally, a device **maximum allowable limit** value (mass of leachable[s]):

**m** = TE x BF x D  BF = benefit factor; D = days in a device category

# Risk Management Evolution: Evolving Tools: Ex TTC

- Threshold of Toxicological Concern (TTC)
  - Emerging concept for medical devices



# Risk Management Evolution: Adverse Events

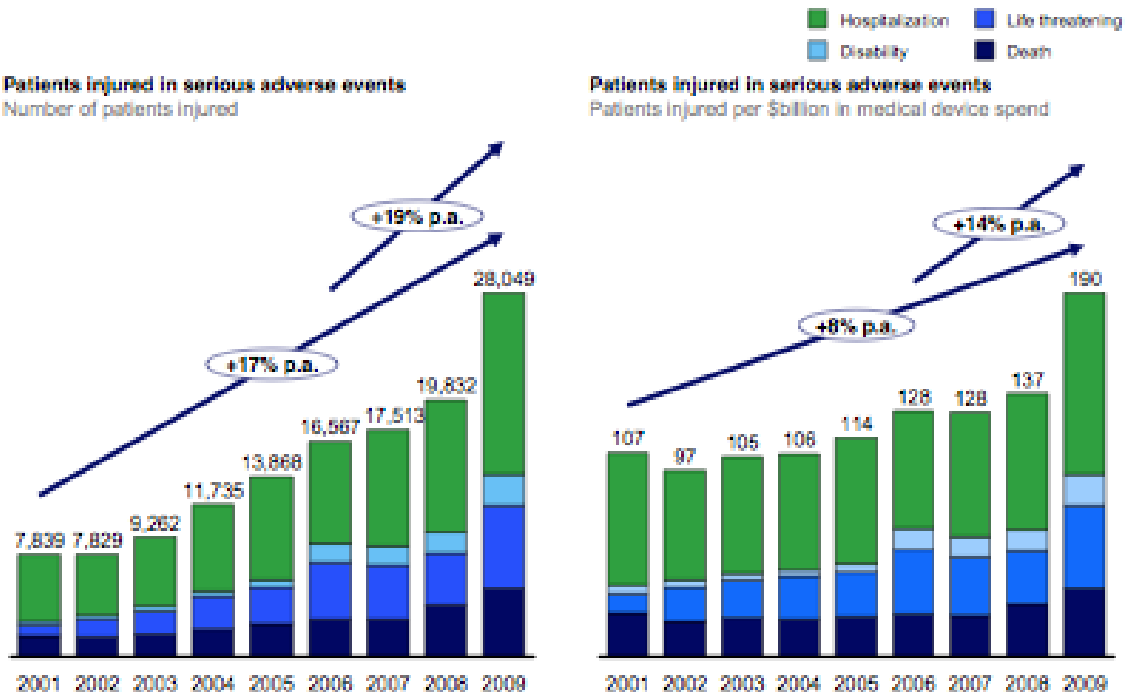
## Serious Adverse Events (SAEs)

- A serious adverse event (experience) or reaction is any untoward medical occurrence that:
  - results in death,
  - is life-threatening,
  - requires in-patient hospitalization or prolongation of existing hospitalization,
  - is a congenital anomaly/birth defect.

*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

# Risk Management Evolution: Device SAE Trends

**Exhibit 5: Total serious adverse event reports adjusted for med device revenues**




* Includes death, life threatening events, hospitalization and disability
Source: Manufacturer and user facilities device experimental (MAUDE) database

[3] Adverse event analysis includes data from the MAUDE database, but excludes data from special exemption summary reporting, such as the Alternative Summary Reporting (ASR) database, the Postmarket Spreadsheet Reports, and Remedial Action Exemptions. Manufacturers may provide batch summary reports to these databases only in certain circumstances; these databases do not include the level of detail included in the primary MAUDE database. If the ASR data had been included here, the combined annual growth rate (CAGR) would have been 24% between 2001 and 2009.
Note: "p.a." means per annum, i.e., per year

# Risk Management Evolution: Reducing SAE's

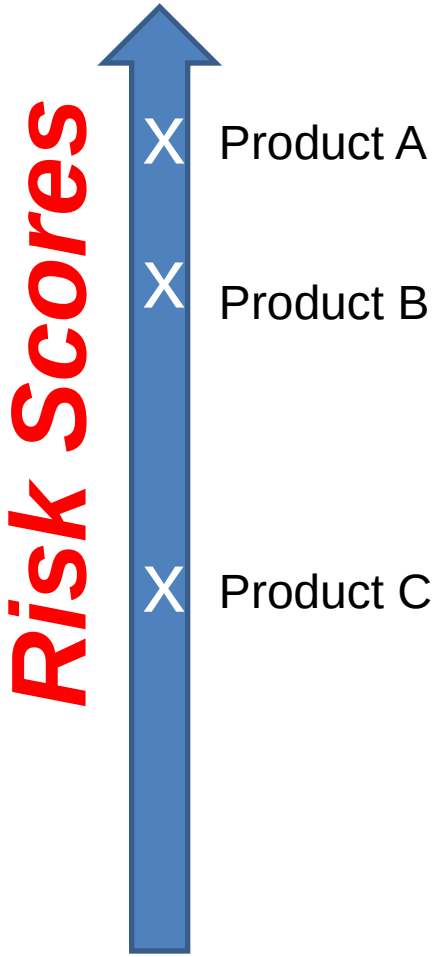
- The medical device industry lacks a prospective risk prediction tool and index
- These tools exist elsewhere; insurance industry uses them to predict:
  - Floods
  - Earthquakes
  - Natural disasters
  - And so on

# Risk Management Evolution: Manufacturers / Users

- Unprecedented challenges
  - Pricing pressures
    - Health care reform / reduced reimbursement / medical device excise tax
    - Competition from emerging markets
  - Reduced R&D pipelines / innovation deficit
  - Regulatory challenges / complexity of approval processes
  - Increasing supply chain complexity and risk
  - Mergers & Acquisitions
  - Others

# Risk Management Evolution: Ex New Risk Scoring Methods

- *Total risk scores based on quantitative elements in a number of categories including:*
  - Testing features and results
  - Therapeutic properties/clinical info
  - Acquisition info (if relevant)
  - API supplier info, spec status, etc
  - Mfg process
  - Supply chain
  - Operational
  - Performance & QC testing
  - Distribution
  - Regulatory compliance
  - Field performance
  - Others
- *Multiple scoring elements in each category leads to overall risk scores*



# Conclusions

- **Device biocompatibility – unique challenges**
- **ISO 10993 Standards promote uniformity, consistency, and patient safety**
- **New tools – new opportunities**
- **Device development experts as risk managers – can aid in reducing SAEs**

# Q & A