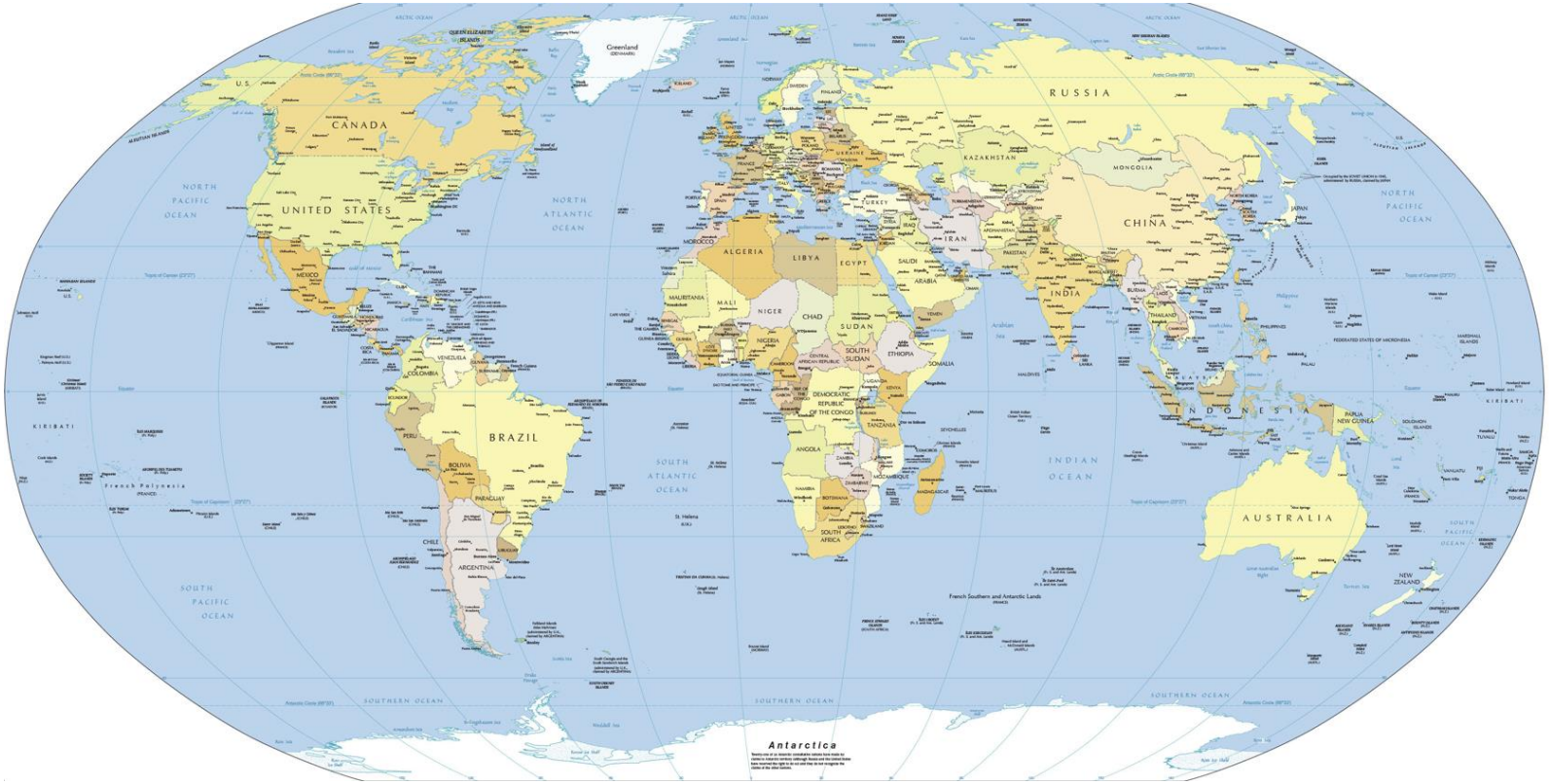
Biocompatibility And Evolution Of Risk Management In Safety Evaluation Of Medical Devices



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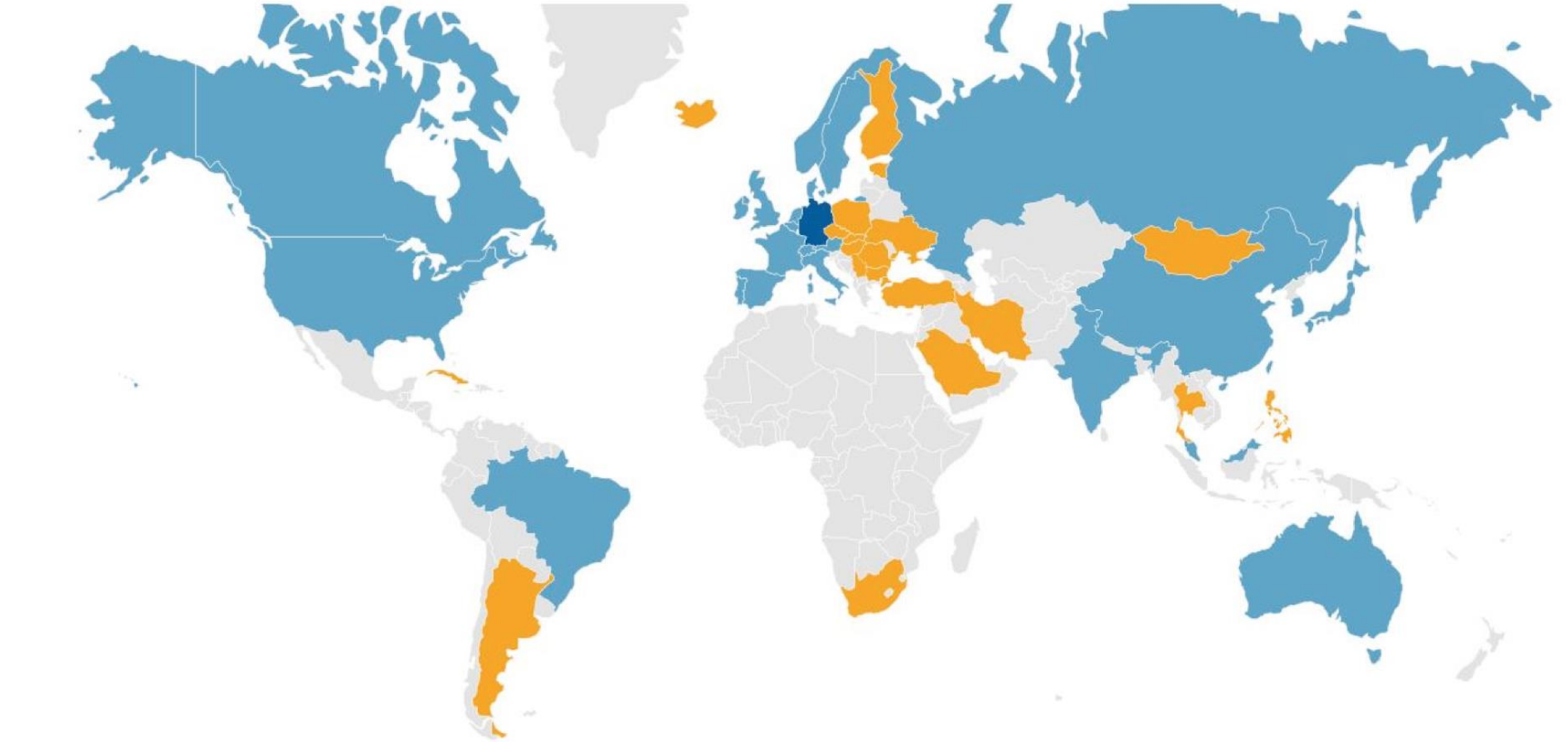
Overview

- ISO TC194 Mission
- Background & History
- ISO TC194 Current Standards
- Risk Management Evolution

ISO TC194 Countries



Secretariat | Participating Countries (24) | Observing Countries (24)

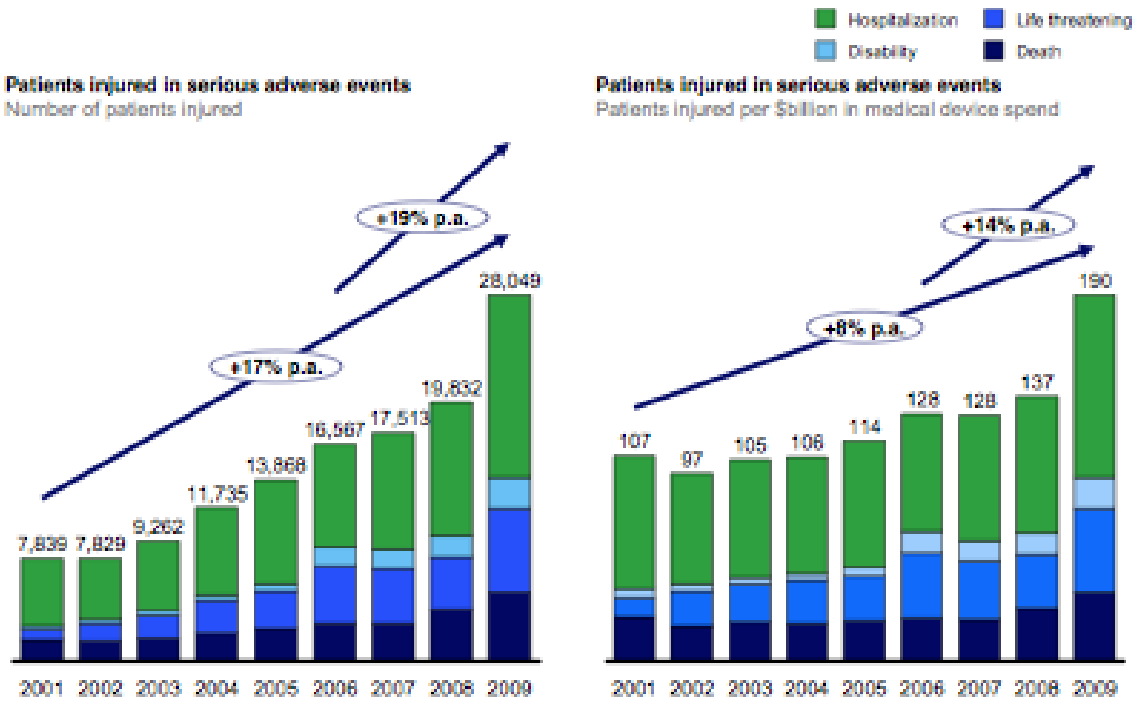
Mission of ISO TC194

TC 194 will contribute 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

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

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

Current - ISO 10993 Part 1

Evaluation within a *risk management* process

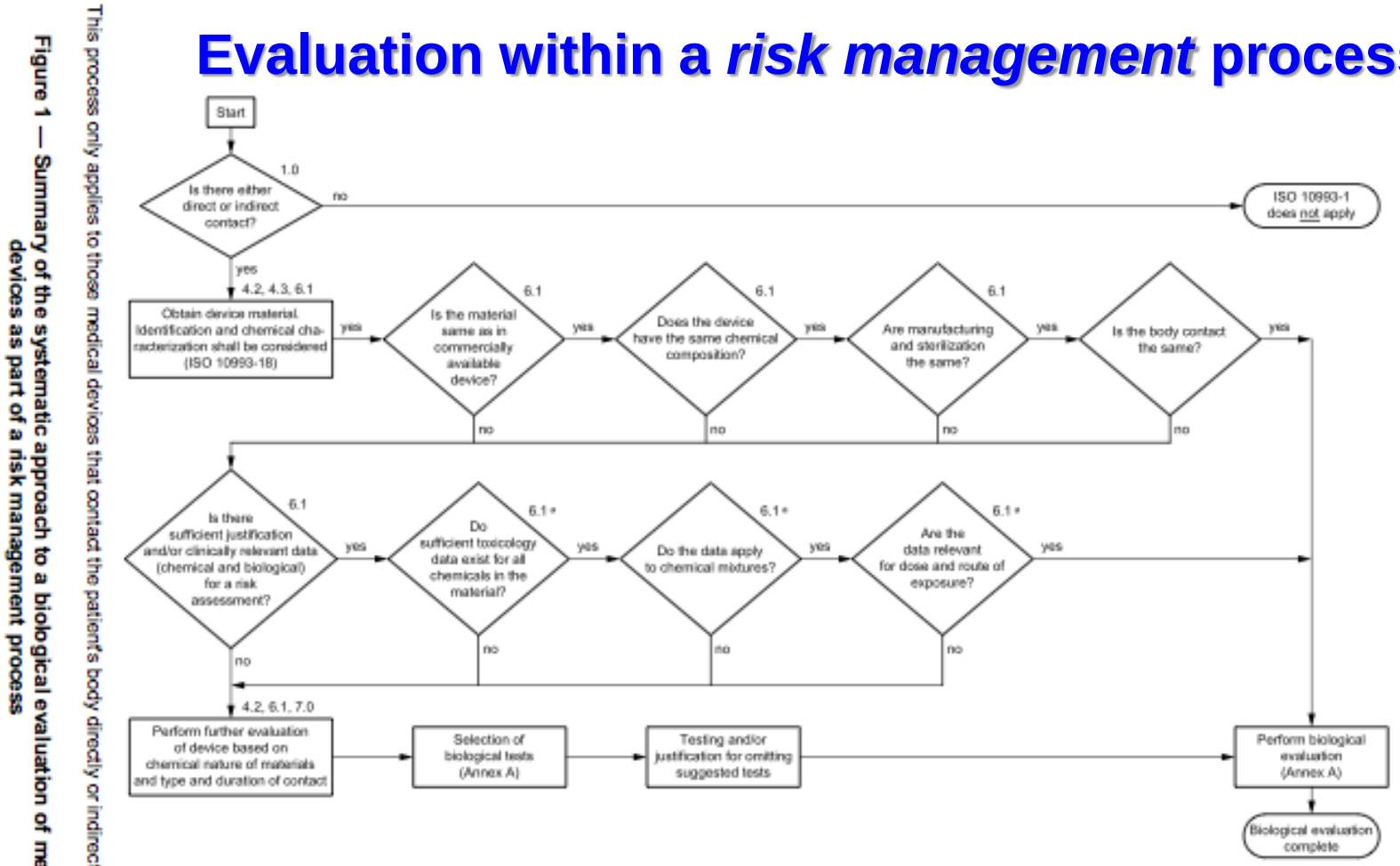


Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

Risk Management Evolution: 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 to 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: 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: 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