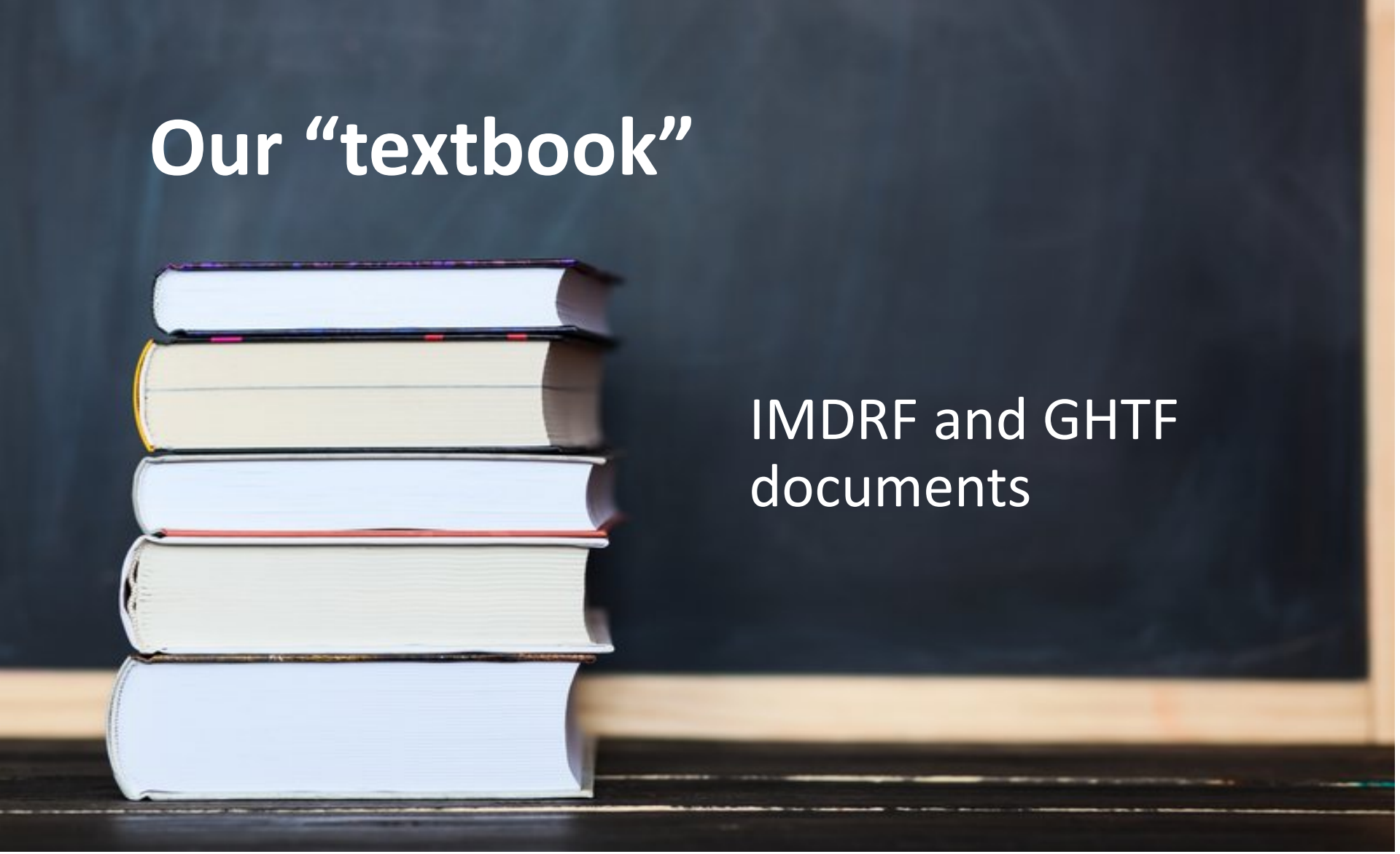
Essential Principles of Safety and Performance of Medical and IVD Devices

Frances Richmond, PhD
Director, DK Kim International Center for Regulatory Science,
University of Southern California

Asia-Pacific Economic Cooperation
USC University of Southern California

Our “textbook”



IMDRF and GHTF documents

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Globalization is challenged by regulatory and quality dissonance

Regulatory dissonance can:

- Increase costs
- Handicap development in less sophisticated societies
- Create non-tariff trade barriers

APEC
Asia-Pacific Economic Cooperation

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IMDRF International Medical Device Regulators Forum

IMDRF is one organization trying to promote harmonization

- Development of harmonized *technical* standards
- Development of harmonized submissions and *data* standards
- Integrated approaches to inspections
  - Regulatory inspections
  - Industry initiatives
- International educational and confidence building opportunities

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IMDRF has a number of overlapping guidances

IMDRF/GRRP WG/N47

Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

7 November 2018

GHTF code: SG3 N15R8 - Date posted: 20 May 2005

GHTF SG3 - Risk Management Principles and Activities within a QMS - May 2005 PDF (130.74 kb)

GHTF code: GHTF/SG1/N77:2012 - Date posted: 2 November 2012

GHTF SG1 Principles of Medical Devices Classification - November 2012

PDF (772.78 kb) DOCX (505.25 kb)

What is a Medical Device?

3.26 *Medical Device*: Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

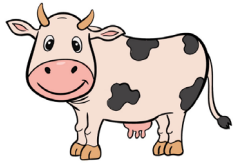
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- investigation, replacement, modification, or support of the anatomy, or of a physiological process,
- supporting or sustaining life,
- control of conception,
- cleaning, disinfection or sterilization of medical devices,
- providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

Definitions seem the same, but detailed considerations often differ…

NOTE 1: Products which may be considered to be medical devices in some jurisdictions but not in others include:

- disinfection substances,
- aids for persons with disabilities,
- devices incorporating animal and/or human tissues,
- devices for in-vitro fertilization or assisted reproduction technologies.



Japan: Regenerative Medicines Product
US: medical devices subclassed as regenerative medicine advanced therapy (RMAT)
EU: Advanced Therapy Medicinal Product

Principles of Device Classification

GHTF code: GHTF/SG1/N77:2012 - Date posted: 2 November 2012

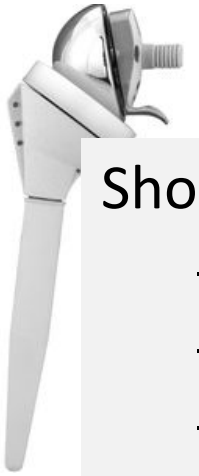
GHTF SG1 Principles of Medical Devices Classification - November 2012

"RAs should establish a device classification system consisting of four classes where Class A represents the lowest hazard and Class D the highest."

Class	Hazard Level	Device Examples
A	Low	Bandages/ tongue depressors
B	Low-moderate	Hypodermic Needles / suction equipment
C	Moderate-high	Lung ventilator / bone fixation plate
D	High	Heart valves / implantable defibrillator

Classifications systems are legacy- vary remarkably

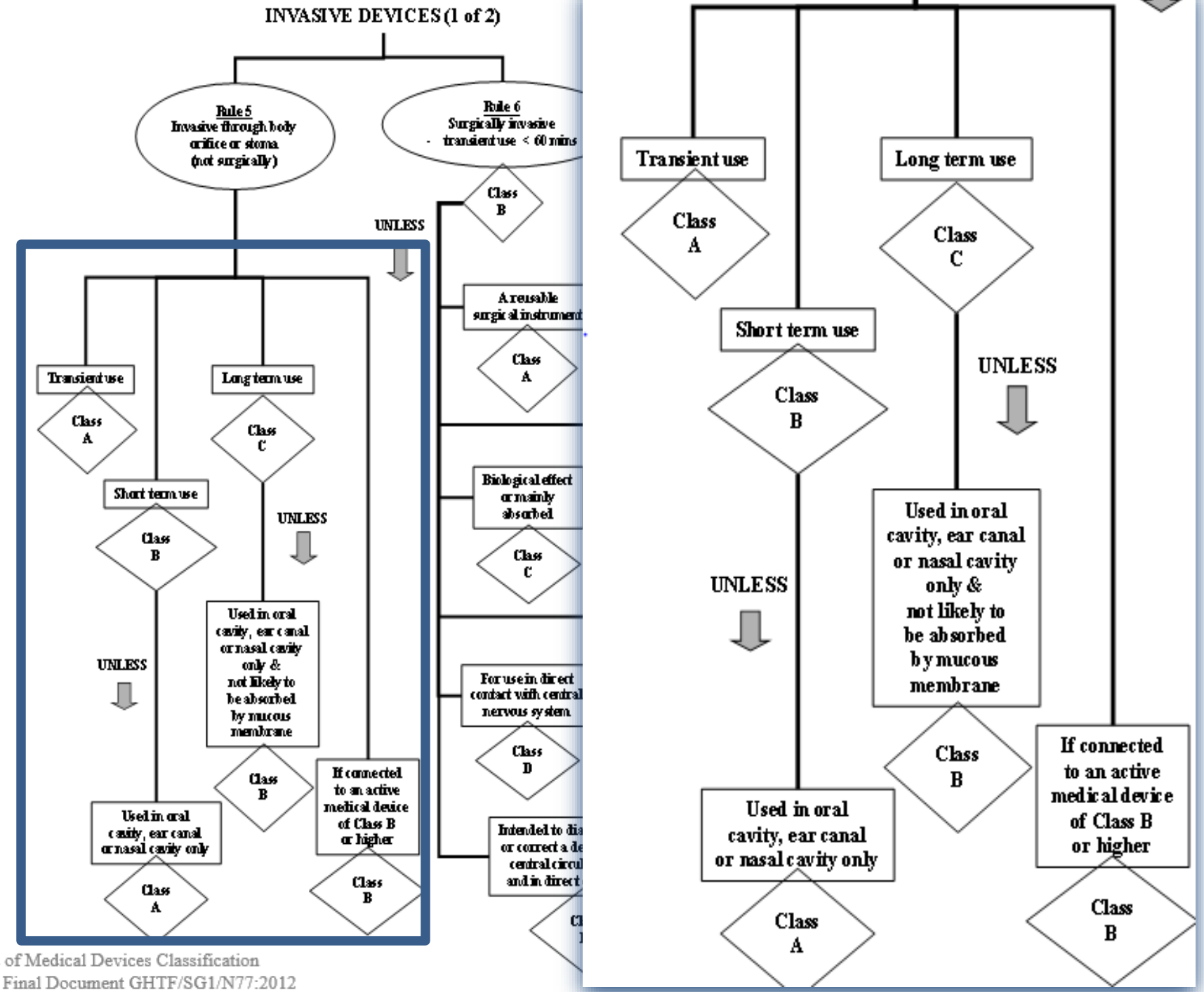
US :	3 classes	I, II, III
Japan:	4 classes	I, II, III,IV
Canada:	4 classes	I, II,III,IV
EU:	4 classes	I IIa, IIb, III
China:	3 classes	I, II, III
Vietnam:	4 classes	A,B,C,D
Thailand:	3 classes	III, II, I
Chile:	4 classes	I, II,III,IV



Shoulder prosthesis:

- Class III in Canada
- Class II in US
- Class III in Japan

Rule 8. All implantable devices, and long-term surgically invasive devices, are in Class C,	Most of the devices covered by this rule are implants used in the orthopaedic, dental, ophthalmic and cardiovascular fields. Example: maxilla-facial implants; prosthetic joint replacements; bone cement; non-absorbable internal sutures; posts to secure teeth to the mandibula bone (without a bioactive coating). **NOTE:** if the device incorporates a medicinal substance in a secondary role refer to Rule 13.
unless they are intended to be placed into the teeth, in which case they are in Class B; or	Examples: bridges; crowns; dental filling materials.
unless they are intended to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class D; or	Examples: prosthetic heart valves; spinal and vascular stents.
unless they are intended to be life supporting or life sustaining, in which case they are in Class D; or	
unless they are intended to be active implantable medical devices, in which case they are Class D; or	Example: pacemakers, their electrodes and their leads; implantable defibrillators.
unless they are intended to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class D; or	Example: implants claimed to be bioactive. **NOTE**: hydroxy-apatite is considered as having biological effect only if so claimed and demonstrated by the manufacturer.
unless they are intended to administer medicinal products, in which case they are in Class D; or	Example: rechargeable non-active drug delivery system.


INVASIVE DEVICES (1 of 2)
Rule 5
Invasive through body orifice or stoma (not surgically)
Rule 6
Surgically invasive
- transient use < 60 mins
Class B
UNLESS
A reusable surgical instrument
Class A
Biological effect or mainly absorbed
Class C
For use in direct contact with central nervous system
Class D
Intended to dis or correct a de central circul and in direct
Transient use
Class A
Long term use
Class C
Short term use
Class B
UNLESS
Used in oral cavity, ear canal or nasal cavity only & not likely to be absorbed by mucous membrane
Class B
UNLESS
Used in oral cavity, ear canal or nasal cavity only
Class A
If connected to an active medical device of Class B or higher
Class B
Transient use
Class A
Long term use
Class C
Short term use
Class B
UNLESS
Used in oral cavity, ear canal or nasal cavity only
Class A
UNLESS
Used in oral cavity, ear canal or nasal cavity only & not likely to be absorbed by mucous membrane
Class B
If connected to an active medical device of Class B or higher
Class B

IMDRF/GRRP WG/N47

Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

7 November 2018

- 13 pages of standards and definitions
- 13 pages of guidance
- About 1 page of guidance for IVDs

Principle:

The manufacturer of a medical device and in vitro diagnostic (IVD) medical device is expected to design and manufacture a product that is safe and effective throughout its life-cycle. This guidance document describes fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance' that, when met, provide assurance that a medical device and IVD medical device is safe and performs as intended, by the manufacturer.

The system builds on risk management

Manufacturers should have a risk management system that extends throughout product lifecycle

- lists both ISO 14971 and 24971 in its relevant standards

Risk control approaches

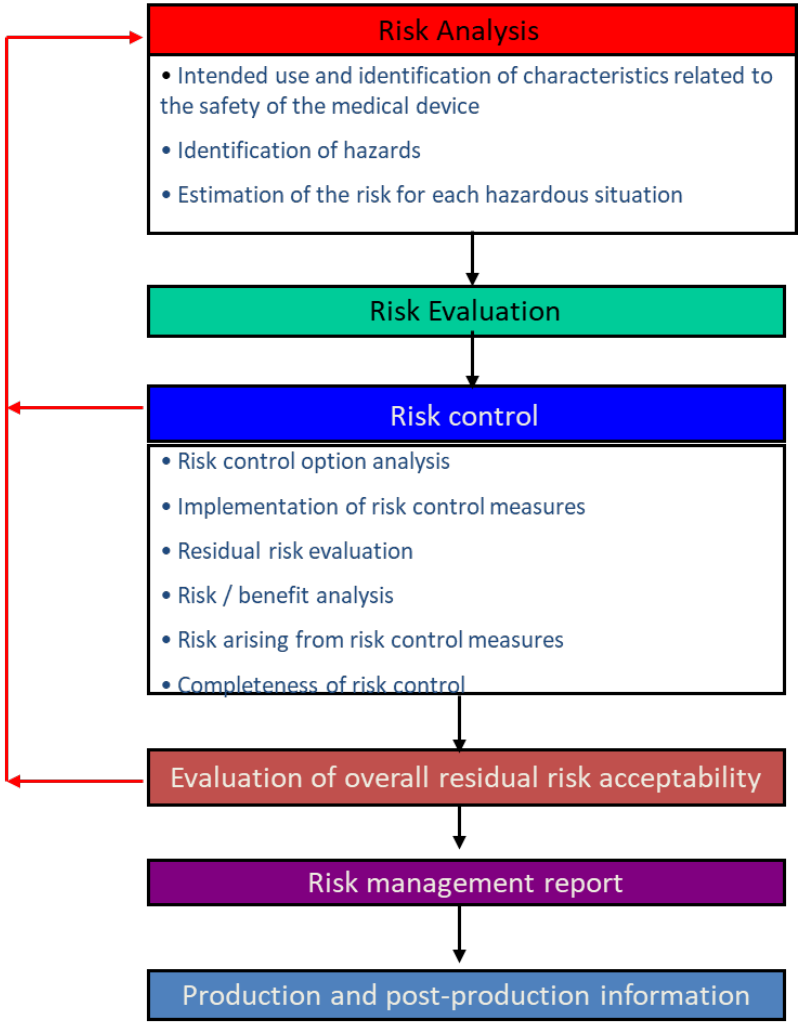
Eliminate

Reduce with protective measures

Warn

Risk Management Basics

1. **Establish** a risk management plan
2. **Identify and Analyze** the known and foreseeable hazards
3. **Estimate and Evaluate** the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse
4. **Eliminate or Control** the risks
5. **Evaluate** the impact of information from the production and postproduction phases, on the overall risk, benefit-risk determination and risk acceptability



Several key sections

- Chemical, Physical and Biological Properties
- Sterilization and Microbial Contamination
- Protection against Electrical, Mechanical and Thermal Risks
- Active Medical Devices
- Protection against Radiation
- Considerations of the Environment and Conditions of Use
- Medical Devices that Incorporate Software
- Medical Devices and IVDs Incorporating Biological Materials
- Medical Devices and IVDs that have a Measuring Function
- Labeling
- Clinical Evaluation (another set of guidances)

Chemical, Physical and Biological Properties

- Materials properties
- Potential to leach toxins
- Infection control for users- human factors
- Packaging to minimize damage and contamination

ISO 10093: Biological Evaluation of Medical Devices

Chemistry

ISO 10993-1, 7, 9, 13, 15, 18,19

- Device Categorization
- Documentation
- Chemical Testing
- Residuals

Biology

ISO 10993, 1-6, 10-12, 20, 33

- Device Categorization
- Hazards Identification
- Biological Testing
- GLP Quality System

Toxicology

ISO 10993, 1 and 17

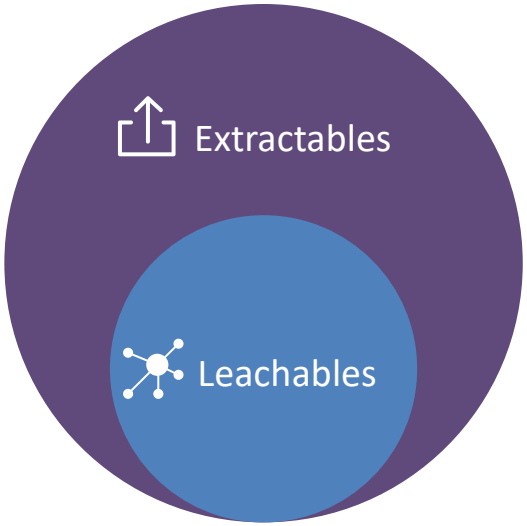
- Hazards Identification
- Exposure Assessment
- Risk Characterization

Common Chemistry Qualification Testing

1

Chemical Characterization (Leachables/ Extractables, and material identification)

What are Extractables and Leachables?



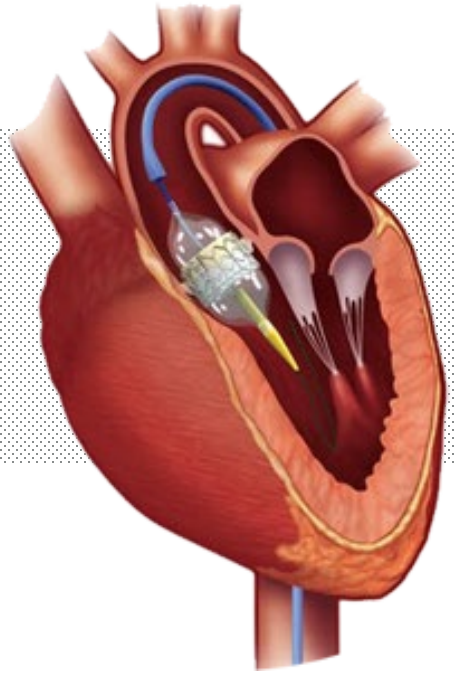
Extractables:

Compounds that migrate from a medical device under **aggressive conditions** such as high temperature, extended contact time, or aggressive solvent system

Leachables:

Compounds that migrate from a medical device under **normal conditions** of exposure (Physiological pH and temperature)

Categorization of Patient Contact



1. Level of Body Contact
   - Blood
   - Tissue
   - Skin
2. Duration of Contact
   - Limited
   - Prolonged
   - Permanent

Testing Matrix

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														
External communicating device	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		

Part of FDA Guidance Document (June 16, 2016)

ISO 10993-1, Table A.1

- It's a framework for the development of an assessment program.
- X's and O's are endpoints for consideration.

Note

Chronic Toxicity, Carcinogenicity, Reproductive and Developmental Toxicity are considered based on risk assessment.

Sterilization and Microbial Contamination

- Design to facilitate cleaning and decontamination
- Assure that packaging will protect and minimize/prevent microbial contamination
- Assure that sterilization methods are appropriate and validated
- Assure that facilities and equipment are appropriate and maintained
- If products are to be sterilized by user, assure that packaging minimizes microbial contamination
- Communicate sterilization status on labeling

Environment and Conditions for Use

- Products to be used with other products should be safe; products near other devices should be safe.
- Special attention should be paid to couplings and connectors
- Design must take environment into account

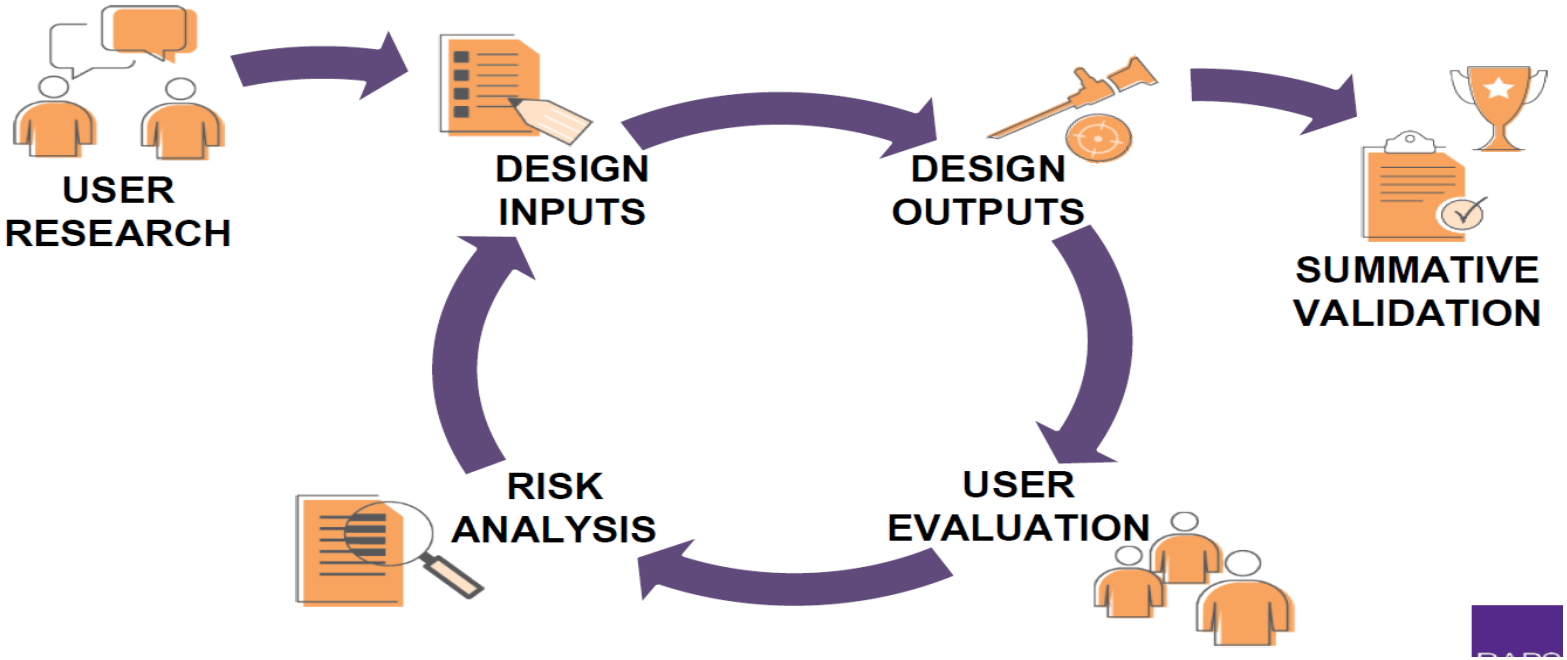
  -electromagnetic, electrical, electrostatic,

  -radiation, pressure, humidity, gases, liquids

  -software- cybersecurity, unauthorized access
- Design must remove or reduce possibility of fire or explosion
- Maintenance, calibration and repair must be safe and easy
- Disposal or recycling should be defined and included in IFU
- Ergonomics and useability are central

Human Factors (HF) Engineering:
How does the user interact with the device?

- Knowledge about human behavior, abilities, limitations and other characteristics must inform the design of medical devices
- User interfaces, systems, tasks, documentation, and training should enhance the safe and effective use of the device



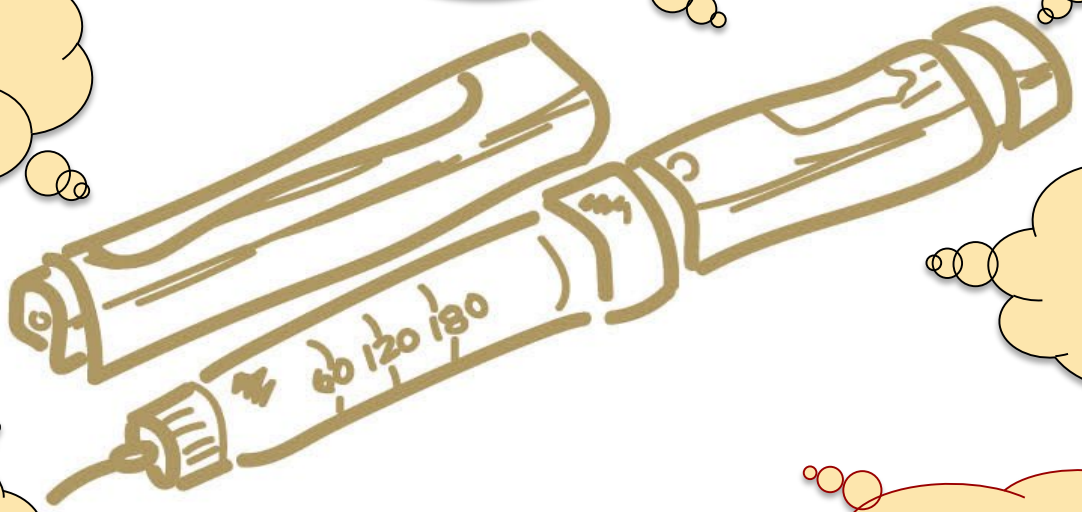
Redmill and Rajan, 1997.

What Could Go Wrong??
Self-Injection Insulin Pen

User not pushing the button all the way?

User with arthritis?

Pediatric user?



Left-handed user?

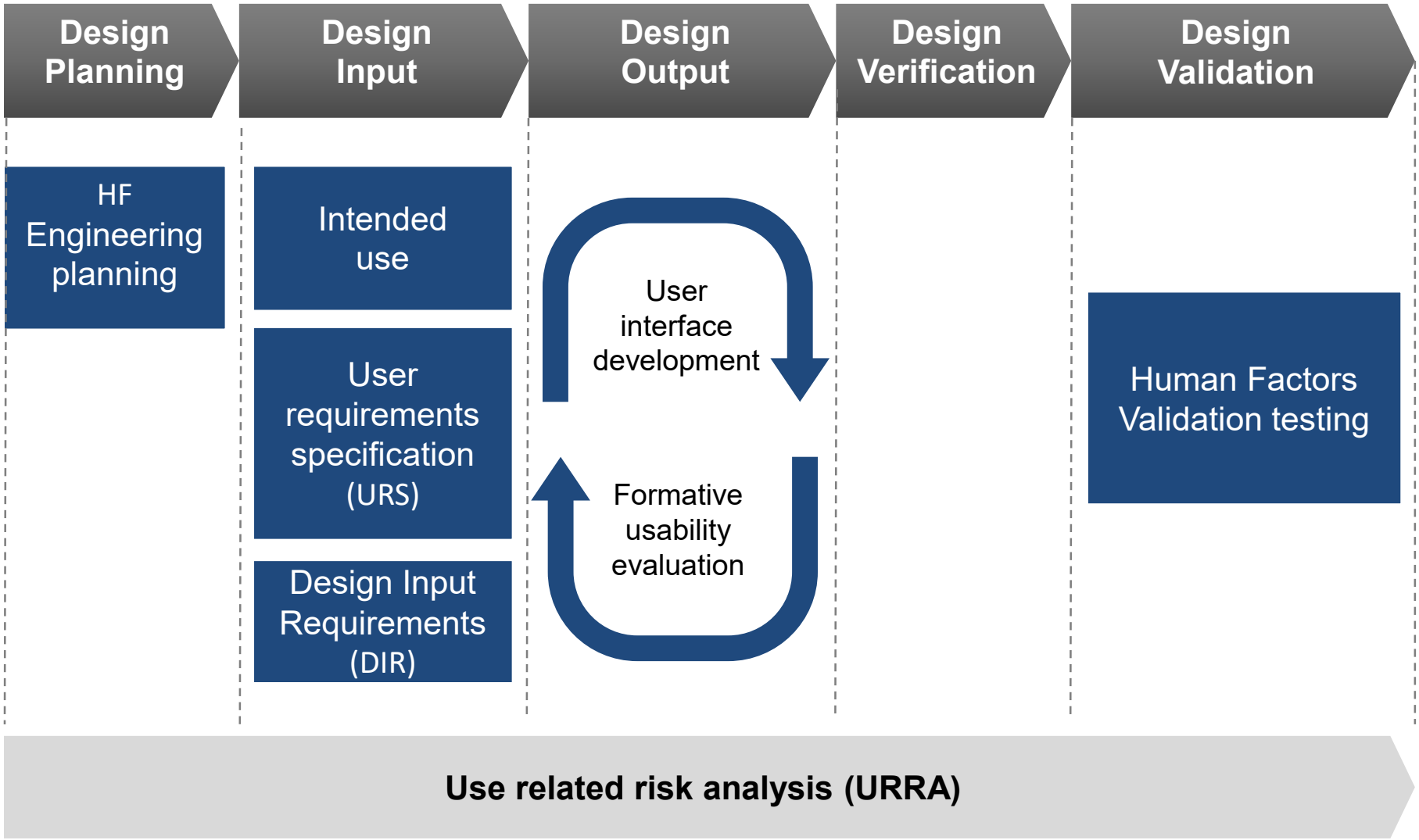
Reuse?

User with colorblindness?

Carry-over effect from previous med?

From Nozomi, 2021

HF Engineering is Integral to Device Development



Diagnostic or Measuring Devices

Key elements relate to performance characteristics

- Accuracy and limits of accuracy
- Standardization of measurement units
- Management of controls and indicators

Another guidance for this, as you saw earlier

In Vitro Diagnostic Devices

- Traceability of calibrators and controls
- Accuracy and precision
- Sensitivity/detection limits
- Specificity
- Specimen stability
- Intended use, users and patient populations

Electrical, Mechanical and Thermal Risks

- Mechanical and vibratory risks
- Noise considerations
- Failure of parts that will be connected and reconnected
- Temperature changes during use that might damage device or surroundings

Protection against Radiation Exposure

- Anticipate
  - conditions of misuse
  - problems in delivery and installation
  - need for visual warnings that radiation is in use
  - Need to control energy distribution and stray radiation

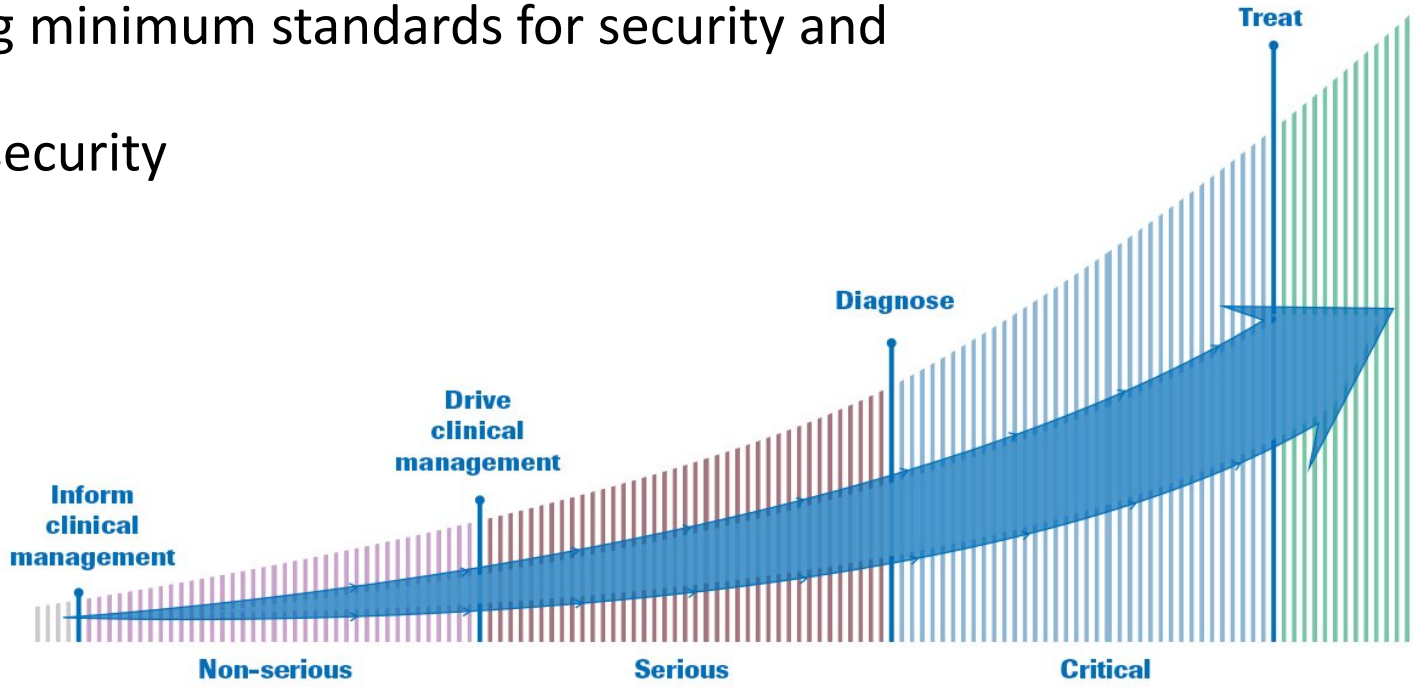
Active Devices and Devices Connected to Them

Key areas of focus

- Mitigating single fault conditions
- Monitoring internal power supplies
- Assuring that external power supplies have alarms for power failures
- Alerting out of range measurements for monitoring devices
- Building in resistance to electromagnetic interference
- Preventing electrical shocks and static discharge damage

Devices with Software or Software as Devices

- Validation
- Accuracy
- Risk management when single faults occur
- Designing for ongoing change
- Accountability for platform restrictions
- Setting minimum standards for security and access
- cybersecurity



Labeling

IMDRF/GRRP WG/N52

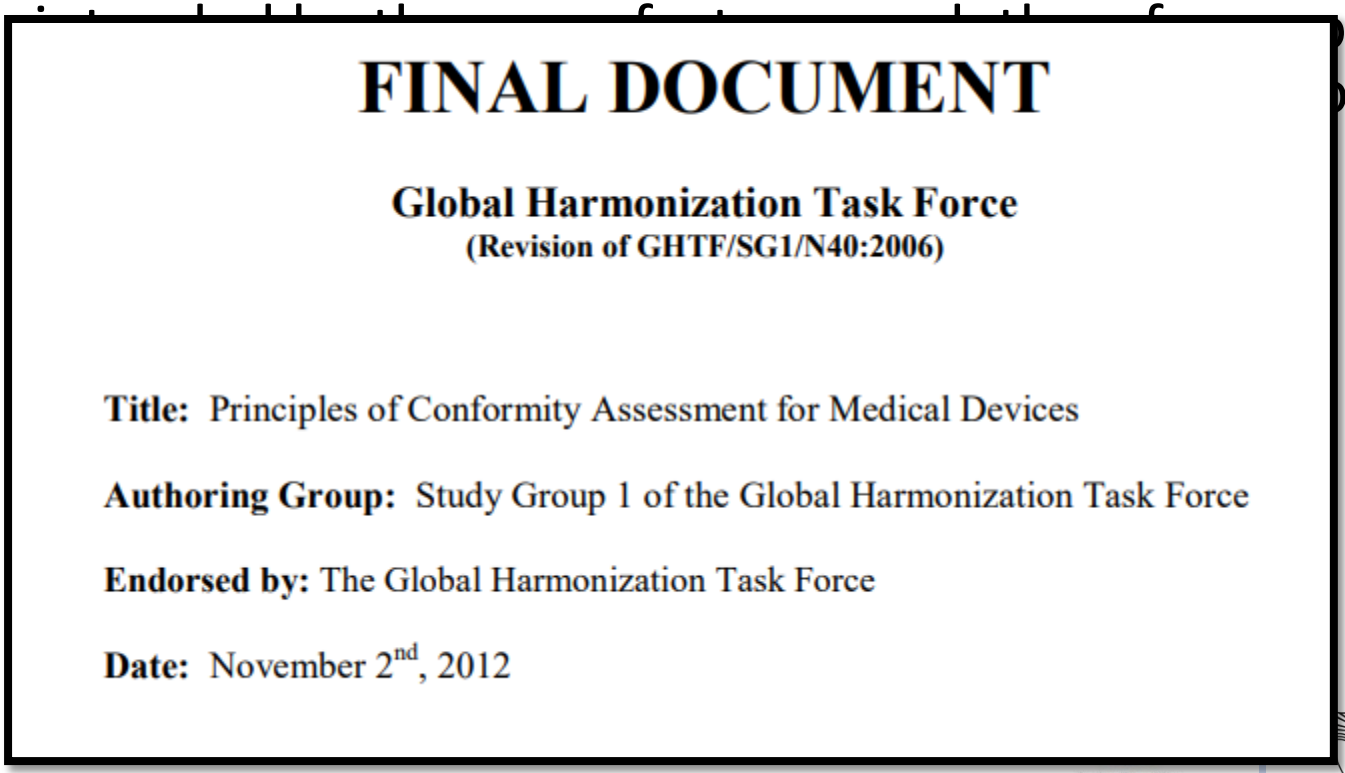
- Identification of and on the device
- Instructions for Use and other instructions

Materials of Biological origin

- Veterinary controls and sourcing
- Management of pathogens and communicable diseases

What is conformity assessment?

The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as
nforms to the
r Medical



FINAL DOCUMENT

Global Harmonization Task Force
(Revision of GHTF/SG1/N40:2006)

Title: Principles of Conformity Assessment for Medical Devices

Authoring Group: Study Group 1 of the Global Harmonization Task Force

Endorsed by: The Global Harmonization Task Force

Date: November 2nd, 2012

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Conformity Assessment looks at key elements

- A quality management system
- A system for post-market surveillance
- Technical documentation
- A declaration of conformity (implicit or explicit)
- Registration of manufacturers and listing of devices

Quality systems regulations may differ but have the same structure

In the US, 21 CFR 820 is the legal basis

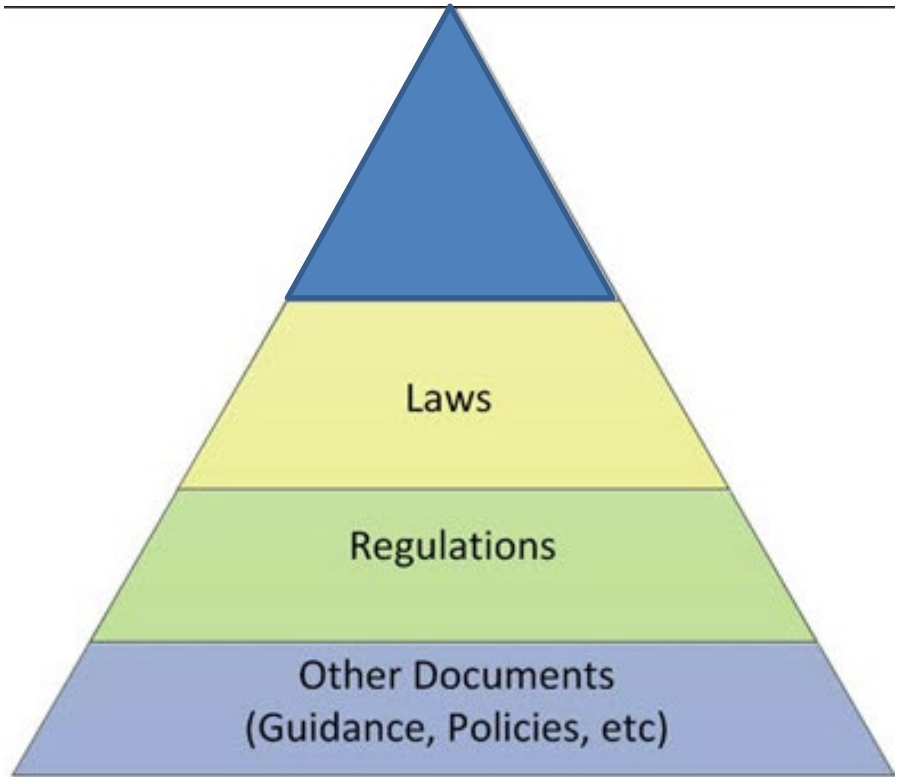
China has “Regulations on the Supervision and Administration of Medical Device”

Many other countries use certification to ISO 13485

Use of Standards

- Standards may be useful but not sufficient
- Standards should be suitable
- Guidance to relevant standards for each section of the document is given in a table.
- Risk management consensus standards
  - importance

Every country has unique rules…



International Standards and Guidances

Many relevant standards listed by section in the Appendix

STED (Summary Technical Documentation)

- Used to demonstrate conformity to Essential Principles
- Recommended as part of submission for Class C and D devices
- Hard to find on-line!

https://www.youtube.com/watch?reload=9&v=6g7uce26rqo

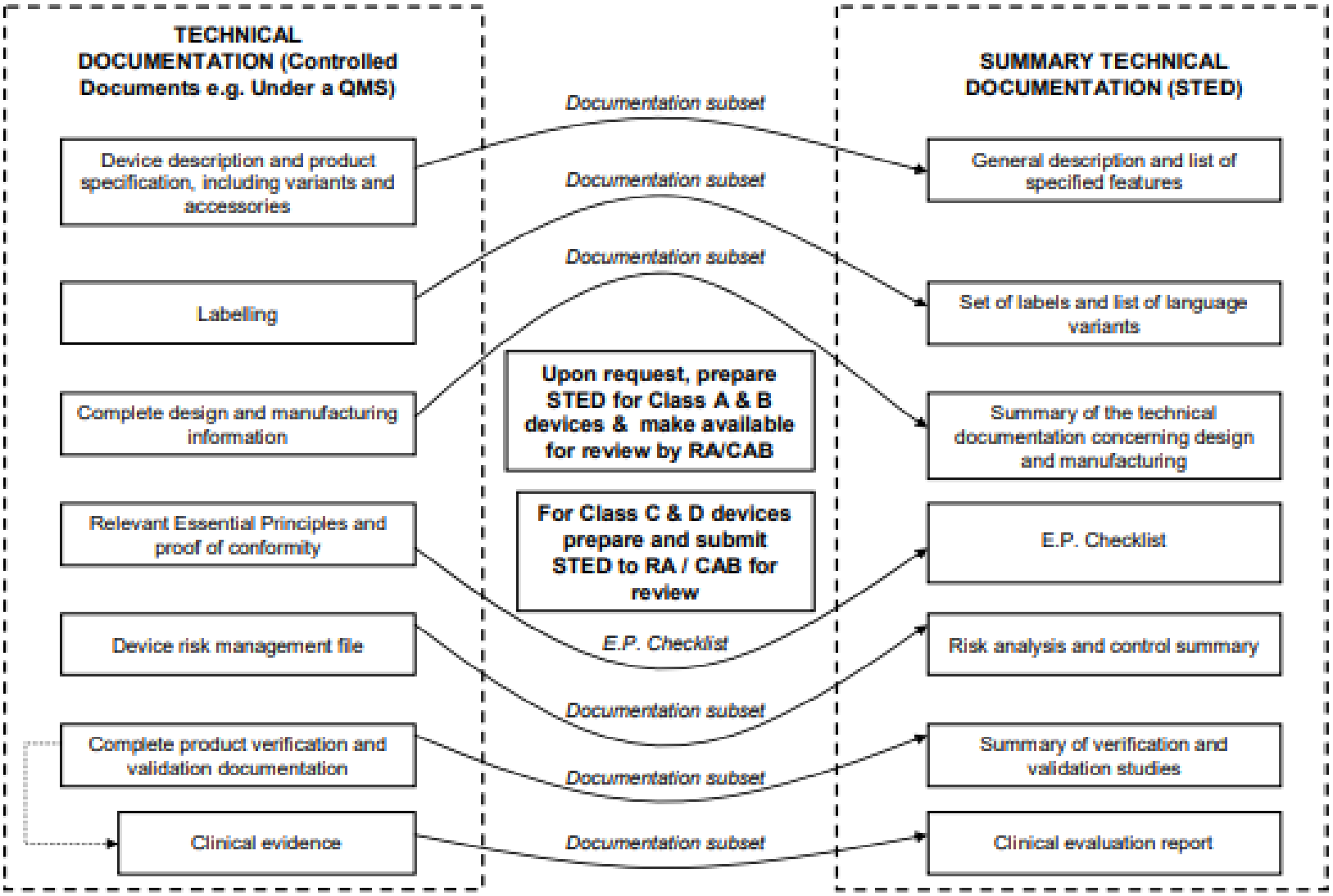


FIGURE 1: PREMARKET USE OF THE STED

Thank You!

감사합니다

Asia-Pacific Economic Cooperation

MEDICAL DEVICES CLINICAL RESEARCH CENTER

순천향대학교 부천병원 SOON CHUN HYANG UNIVERSITY HOSPITAL BUCHEON

순천향대학교 SOON CHUN HYANG UNIVERSITY

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