The Essential Principles of Safety and Performance

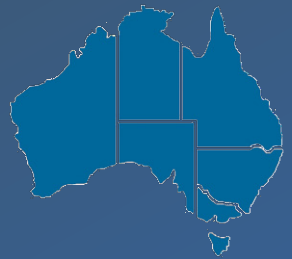
Michael Flood FIEAust CPEng(Biomedical) NER Apec Engineer Int PE(Aus)
Locus Consulting P/L
AUSTRALIA


In a Global Context

A little about me

.....

- Biomedical Engineer
- Over 40 years in the medical devices sector of Healthcare Industry
  - 8 years in commercial organisation – technical marketing and service engineering
  - 10 years public health sector – engineering services, asset acquisition and management
  - 17 years with TGA as the industry regulator
  - 10 years consulting back to all three sectors



International activities

- GHTF
  - SG 2 – postmarket – 1996 – 1999
  - SG 1 – premarket – 2000 – 2009
- GMDN – Maintenance Agency Policy Group – 2000 – 2008
- ISO – Represent Australia on TC 150 – Surgical Implants
- Liaison with EU Commission and Notified Bodies on behalf of TGA
  - Conformity Assessment & market entry
  - EU Australia Mutual Recognition Agreement
- AHWP, ASEAN and APEC Conferences and Workshops
  - 2002 through 2018, and now .....
- Consultant to WHO, UN and ASEAN on medical device regulation
  - Introduction of regulation in developing countries
- Standards Australia
- Engineers Australia
- Visiting Lecturer – several universities – regulatory affairs

The Essential Principles ……..their origin

- EU Medical Device Directive 93/42/EEC – Annex I
  - Essential Requirements
- GHTF SG1 - commences work on premarket framework – 1994
  - GHTF – SG1/N11/R20:2005 >>>> finally N77/:2012
    - Essential Principles of Safety and Performance of Medical Devices
- AHWP – AHWP/WG1a/F002:2013
  - Essential Principles of Safety and Performance of IVD Medical Devices

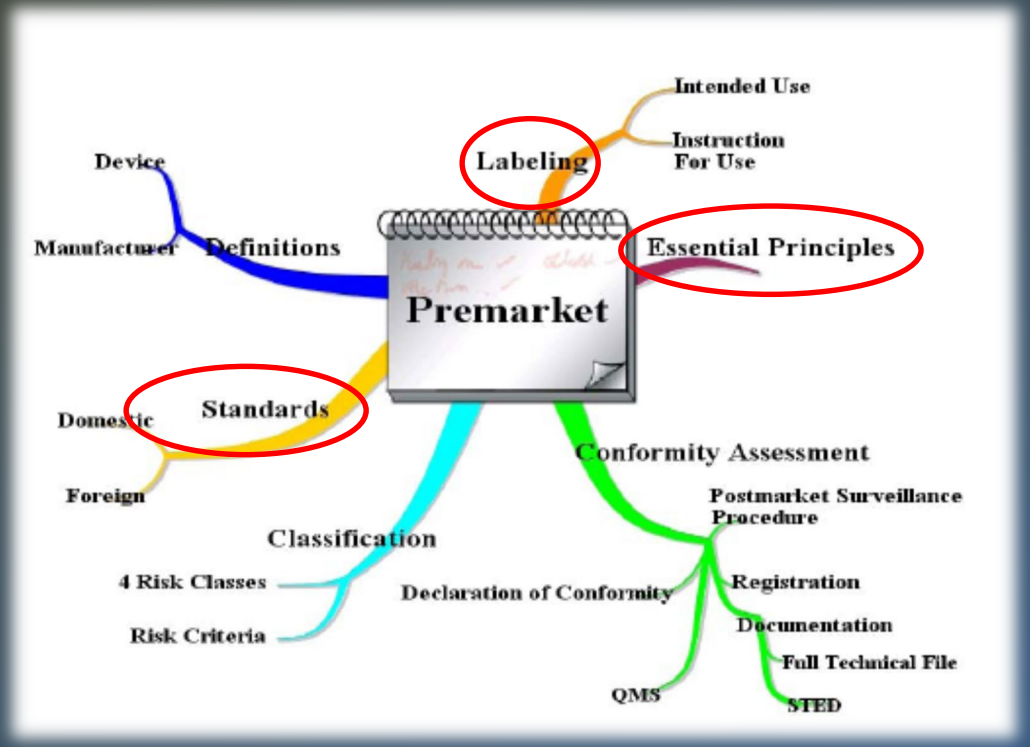
Over the years .....

- Canada - Medical Device Regulations 1998 - Part 1
  - Safety and Effectiveness Requirements
- Japan – Medical Device regulations – 2000
  - Essential Principles
- Australia – Therapeutic Goods (MD) Regulations 2002 – Schedule 1
  - Essential Principles
- ASEAN Medical Device Directive:2015
  - Essential Principles of Safety and Performance

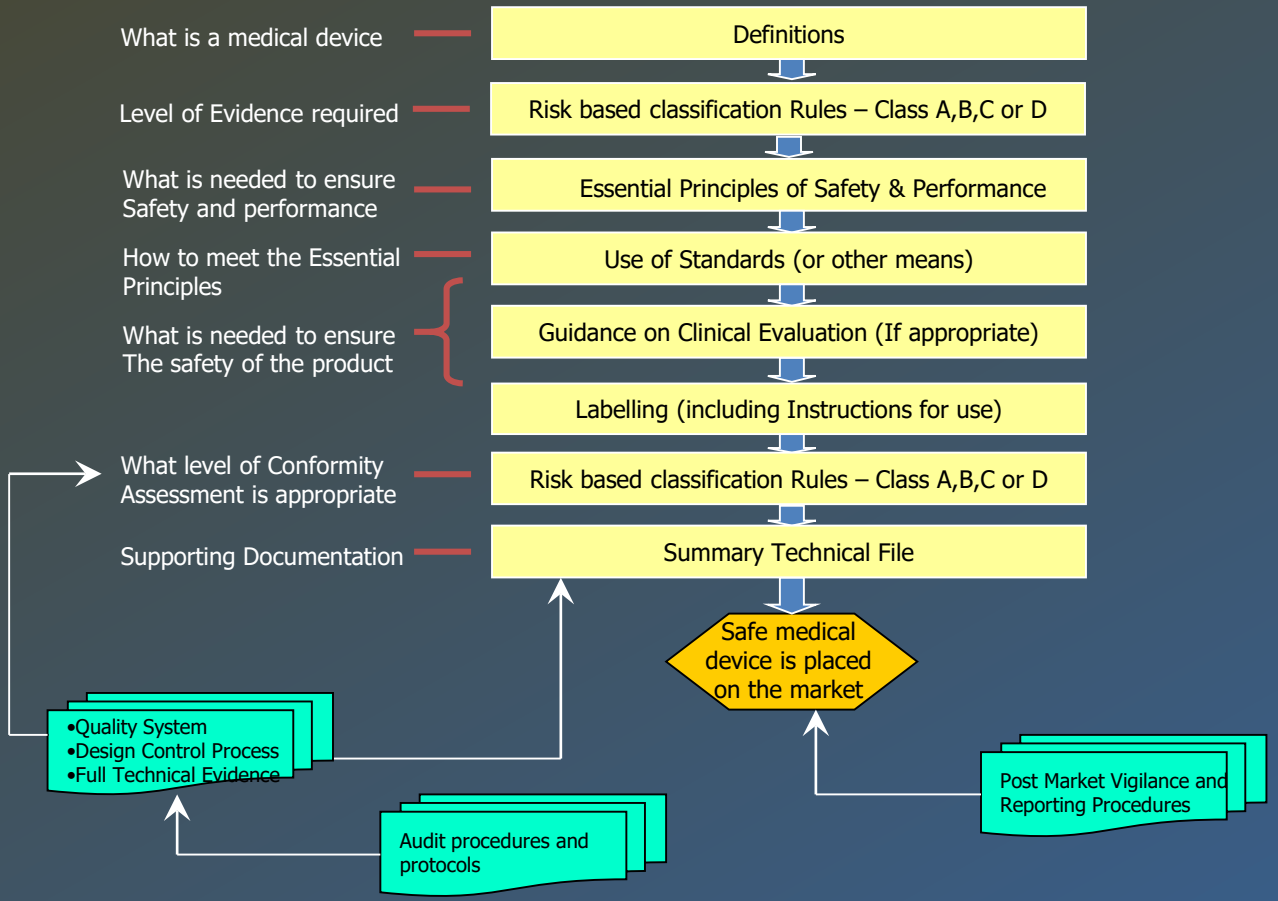
Over the years .....

- EU – Medical Device Regulations 2016
  - Annex I - General Safety and Performance Requirements
- India - Medical Device Rules 2017
  - Chapter 2, Rule 6 – Essential Principles for manufacturing medical devices

Pre-Market Requirements



Pre-Market Requirements



Importance of Essential Principles

- "Consistent identification, selection and application of safety and performance principles to a medical device offers significant benefits to the manufacturer, user, patient or consumer, and to Regulatory Authorities since it allows its manufacturer to design, manufacture and demonstrate the device is suitable for its intended use. …"

- "… Moreover, eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments."

  - GHTF/SG1/N77:2012 - Essential Principles of Safety and Performance of Medical Devices

Essential Principles

— Relate to safety and performance,

— Are applicable to all devices, independent of the risk class, and

— The principles are not objective pass/fail criteria

Essential Principles

- Six general principles
  - Applicable to all medical devices
- Ten relating to design and construction
  - Some only applicable, depending on the technology used
- One for information accompanying a device
  - Applicable to all devices
  - Labelling and instructions for use.
- One relating to the form of clinical evidence
  - Applicable to all devices
  - Refers to the method for generating clinical evidence
    - The Declaration of Helsinki.

Essential Principles

- Essential Principles lay down the necessary elements for protecting the public interest e.g. health, safety and environmental issues i.e. all that is necessary to achieve objective of regulatory framework
- They define the results to be attained or the hazards to be dealt with, they do not specify the technical solutions to be adopted
- They are not based on technical requirements and are not affected by technological progress or innovation. Consequently, they are not frequently subject to regular revision.
- They are mandatory when applicable. Rationales for non-compliance are not an option

Essential Principles

- From a technical perspective they are the most important aspect of any regulatory framework
- Compliance to EP's is based on principle of "presumption of conformity"
  - Comply with relevant standards → comply with EP's
  - Ref to the hierarchy of standards
- EP's 1-6 are general requirements, focus is on safety and performance taking risk and risk benefits into consideration
- EP #2 includes "state of the art" requirement
  - EP's don't change but "state of the art" does
  - Products/files should be maintained in line with development of new requirements/standards etc.

Purpose

- "To describe six **general requirements** of safety and performance that apply to all medical devices.

- "… These are grouped as:
  - Safety principles
  - Risk to patient, user or environment and risk/benefit
  - Performance
  - Transport and storage
  - Labelling and IFU
  - Clinical Evidence and/or performance

- The manufacturer selects which of the design and manufacturing requirements are relevant to a particular medical device, documenting the reasons for excluding the others.

- The Regulatory Authority and/or Conformity Assessment Body may verify this decision during the conformity assessment process." (or audit)

Purpose

- To provide a comprehensive list of **design and manufacturing requirements** of safety and performance, some of which are relevant to each medical device. …"

- "… These are grouped as:
  - Chemical, physical and biological properties
  - Infection and microbial contamination
  - Manufacturing and environmental properties
  - Devices with a diagnostic or measuring function
  - Protection against radiation
  - Requirements for medical devices connected to or equipped with an energy source
  - Protection against mechanical risks …

Demonstrating conformity

- The tools –
  - Selected standards (ISO, IEC, EN, etc)
    - EU – ‘Harmonised’ standards
    - AHWP – ‘Recognised’ standards
    - ASEAN – ‘Recognised’ Standards
  - Manufacturer test protocols
    - In the absence of a relevant standard
  - Clinical Evidence

A couple of examples ……

2 Design and construction of medical devices to conform with safety principles

(1) The solutions adopted by the manufacturer for the design and construction of a medical device must conform with safety principles, having regard to the **generally acknowledged state of the art**.

(2) Without limiting subclause (1), in selecting appropriate solutions for the design and construction of a medical device so as to minimise any risks associated with the use of the device, the manufacturer must:

(a) **first, identify hazards and associated risks** arising from the use of the device for its intended purpose, and foreseeable misuse of the device; and

(b) **second, eliminate, or reduce, these risks as far as possible** by adopting a policy of inherently safe design and construction; and

(c) **third, if appropriate, ensure that adequate protection measures are taken**, including alarms if necessary, in relation to any risks that cannot be eliminated; and

(d) **fourth, inform users of any residual risks** that may arise due to any shortcomings of the protection measures adopted.

“State of the art”

“The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the **generally acknowledged state of the art**.”

- How do we determine the current “state of the art”?
- How does the state of the art change over time?
- How does post-market surveillance help establish the state of the art?

“State of the art”

- ISO 14971, Annex D (informative)
  - *“State of the art” is used here to mean what is currently and generally accepted as good practice. Various methods can be used to determine "state of the art" for a particular medical device. Examples are:*
  - *– standards used for the same or similar devices;*
  - *– best practices as used in other devices of the same or similar type;*
  - *– results of accepted scientific research.*
  - *State of the art does not necessarily mean the most technologically advanced solution.*

“State of the art”

- Using fundamental principles is the easiest way for manufacturer to confirm device is ***“state of the art”*** as required

- *“state of the art”* not defined by, but companies may internally define it as:

Term used to signify that the device design, construction and technical documentation is considered to be up-to-date. In practical terms, for a device described as "state of the art," the following aspects should be considered:

- *current harmonized standards have been used to demonstrate conformity with the Essential Principles*
- *the device's technical documentation (Design Dossier or Technical File) is an accurate reflection of the device and manufacturing/quality system processes*
- *the device risk management and clinical documentation is up to date, based on device / relevant general experience*

Note: *"state of the art" does not necessarily mean the most technologically advanced solution; the device technology and manufacturing processes applied should be considered relatively modern and generally should not encompass use of obsolete technology.”*

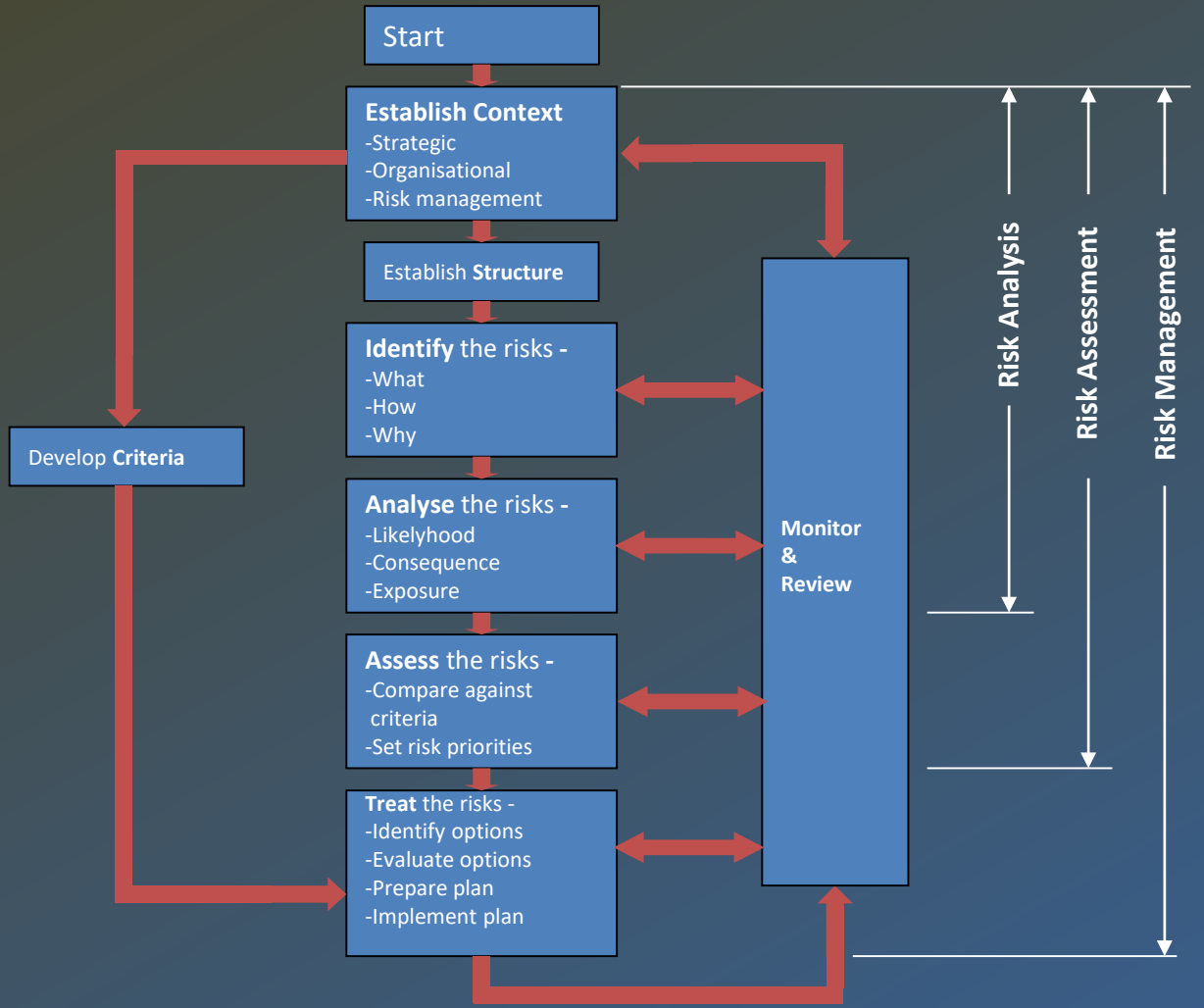
Risk Management

The systematic application of management policies, procedures and practices to the task of

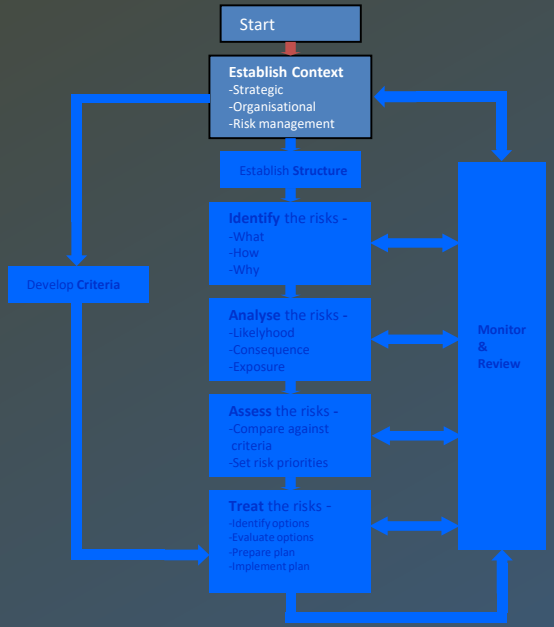
- Identifying,
- Analysing,
- Assessing,
- Treating and
- Monitoring…… of risk

??? Demonstrate compliance

ISO 14971:2007 - Medical devices - application of risk management to medical devices

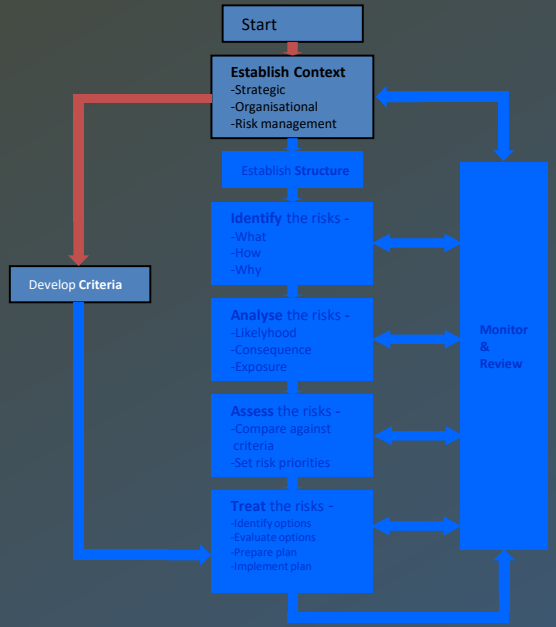

Start
Establish Context
-Strategic
-Organisational
-Risk management
Establish Structure
Identify the risks -
-What
-How
-Why
Analyse the risks -
-Likelyhood
-Consequence
-Exposure
Assess the risks -
-Compare against criteria
-Set risk priorities
Treat the risks -
-Identify options
-Evaluate options
-Prepare plan
-Implement plan
Develop Criteria
Monitor & Review
Risk Analysis
Risk Assessment
Risk Management

Context



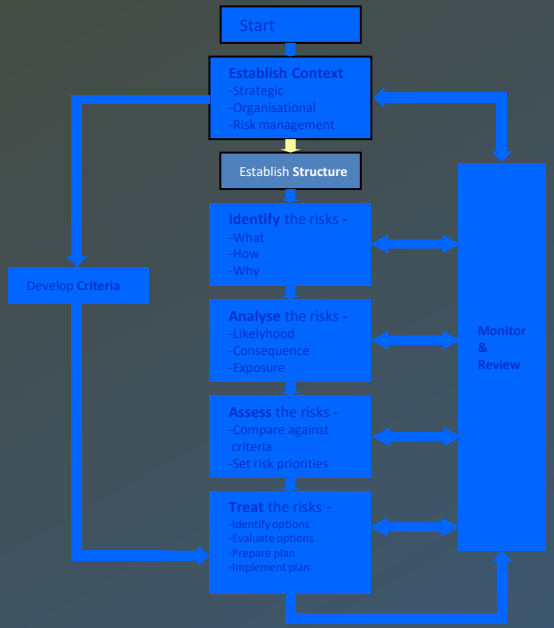
- Inventory
- Stakeholders
  - Institution
  - Clinical Staff
  - Patient
  - Supplier
- Accreditation
- Standards
- Financial
- Management
- Statutory/Regulatory
- Legal

Assessment Criteria



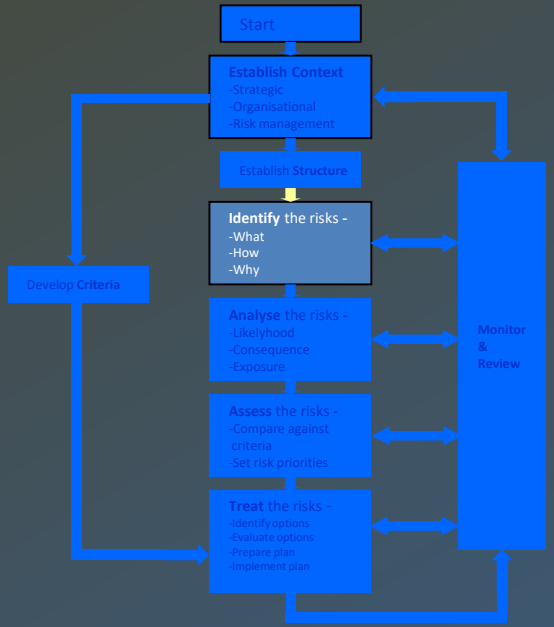
- Impacted on by
  - Operational
  - Technical
  - Financial
  - Legal
  - Social
  - Humanitarian
  - and Other criteria

Structure



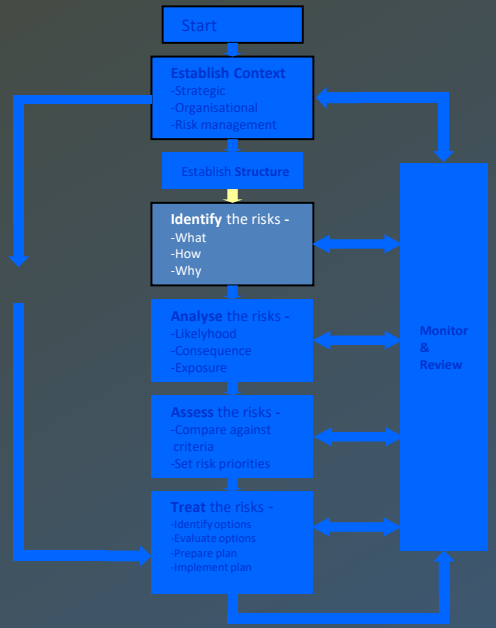
- Develop a logical framework for identification and analysis of risk

Identify the Risks



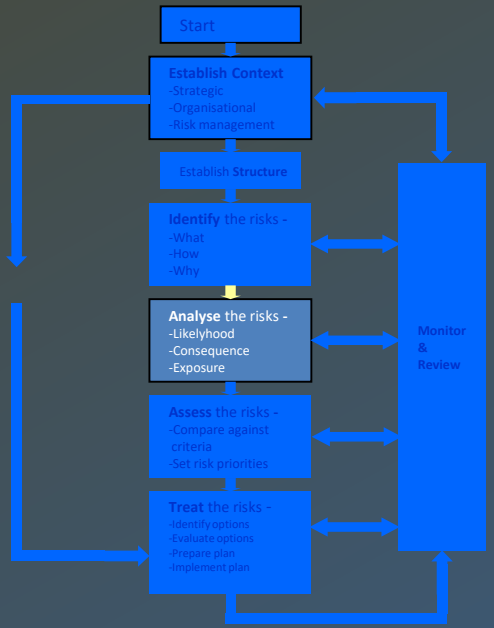
- to –
  - Patient
  - Clinical Staff
  - Equipment
  - Infrastructure
- The
  - **What**
  - **Why**
  - **How**

Tools and techniques



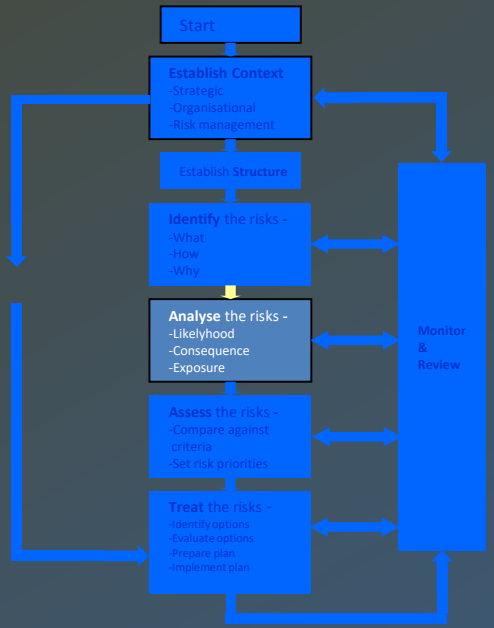
- Checklists
- Flow charts
- Brainstorming
- Systems Analysis
- Scenario analysis
- Systems engineering techniques
- **Records**
- **Judgements based on experience**

Risk Analysis



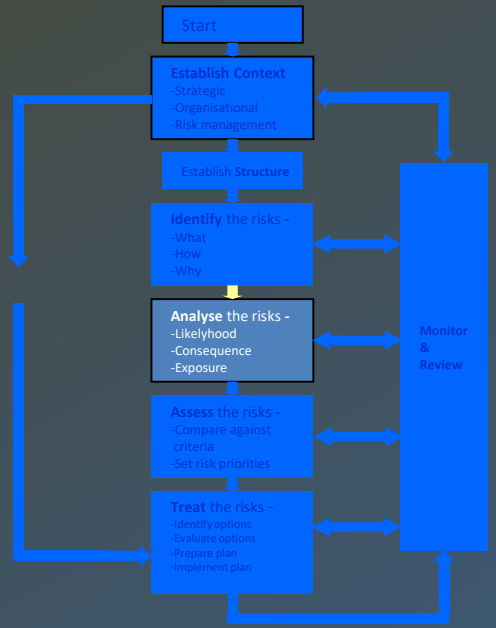
- **Risk = Likelyhood x Consequences**
  - (in the context of existing control measures)

Consequences



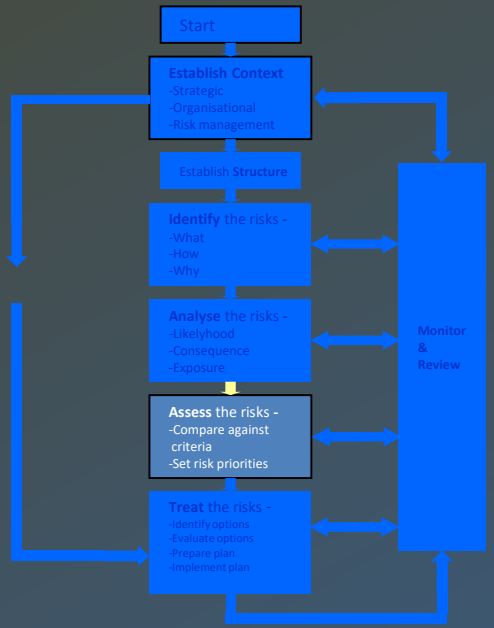
- Failure is unlikely to result in serious consequences
- Failure will have significant impact on patient care, but would not be likely to cause direct serious injury
- Life support, key resuscitation devices, and others wher failure is likely to result in serious injury to patients or others

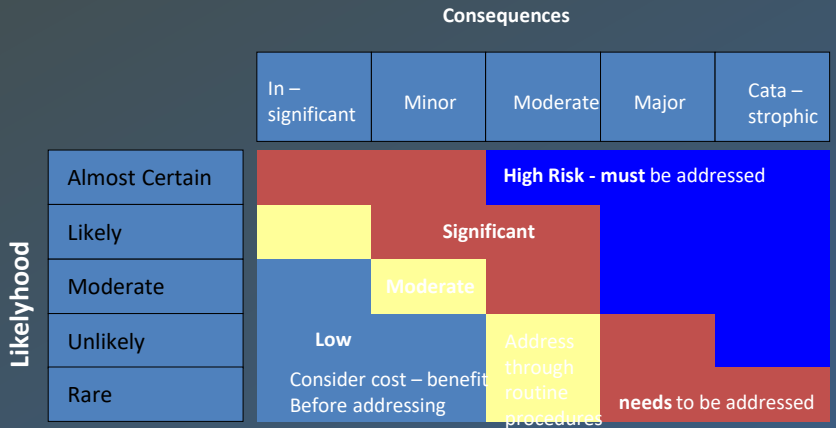
Likelyhood



- Historical failure rate (records)
- Can the failure be detected by the user before the hazard occurs
- Will misuse increase the likelihood of failure
- Are alarms in place to alert the user in the event of failure
- Can the failure be eliminated by preventive maintenance

Assess the Risk





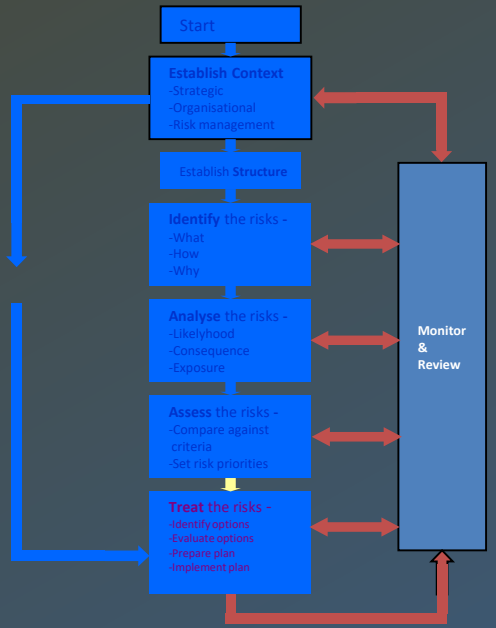
Risk Treatment

- Identify range of options
- Evaluate the options
- Prepare Risk Treatment Plan
- Implement plan

- Document Residual Risk


Polarity/Non-Polarity

Monitoring & review



- Few risks remain static !!
- Review is an integral part of any risk management treatment plan

Standards

- ISO/IEC Guide 51 -.....
- ISO 9000 – Quality Systems
- ISO 13485 – Quality management systems – Mfr of medical devices
- ISO 14971-1 – Medical Devices – Risk management – Application of risk analysis
- ISO 31000 Series – Risk management

Demonstrating conformity

- **Harmonised Standards**
- **Recognised Standards**
  - A recognized standard gives technical expression to the Essential Principles
  - Regularly revised to maintain ‘state of the art’
  - However, compliance **not** mandatory
    - in order not to restrict technological innovation, more flexible regulatory solutions.

- However……. Compliance to a recognised standard is by far the easiest route to demonstrating compliance to EP’s

Demonstrating conformity

- Lists of harmonised/Recognised standards are published by regulators

- For example -
  - EU – Standards are published by CEN/CENELEC as EN documents
    - Eg EN ISO 14971:2102
  - ASEAN – List published by ASEAN Medical Devices Committee
  - AU – Lists published in Medical Device Standards Orders
  - SFDA – Draft list out for comment/consideration

Demonstrating conformity

- **Presumption of Conformity**
  - Compliance with Harmonized/Recognised Standards presumes conformity to an element of the Essential Principles

Clinical Evidence and Standards - examples

For all medical devices, the demonstration of conformity with essential principles includes a clinical evaluation in accordance with GHTF guidance. The clinical evaluation should review clinical data in the form of any:

- clinical investigation reports,
- literature reports/reviews, and
- clinical experience.

to establish that a favourable benefit-risk ratio exists for the device.

Note: Further information is provided in GHTF/SG5/N2R8:2007 *Clinical Evaluation*. Clinical investigations on human subjects should be carried out in accordance with the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results. In addition, some countries may have specific regulatory requirements for pre-study protocol review or informed consent.

See GHTF/SG5/N3:2010 *Clinical Investigations*

Clinical Evidence and Standards - examples

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See GHTF/SG5/N3:2010 *Clinical Investigations*

Clinical Evidence and Standards - examples

- Process focus -
  - EN 540 – Clinical investigation of medical devices for human subjects
  - ISO 14155 – Clinical Investigation of medical devices
- Device focus -
  - ISO 5840 – Cardiovascular implants - Cardiac valve prostheses - clause 9
  - ISO 11979-7 – Ophthalmic Implants - Intraocular lenses - clinical investigations

Clinical Evidence and Standards - examples

- Not a standard, but

MEDDEV 2.7/1 Revision 4, June 2016

CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

is gaining recognition as a template for development and presentation of clinical data and review presented in a Clinical Expert Report within a STED or CSDT

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CLINICAL EVALUATION:
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Purpose

- To provide a comprehensive list of **design and manufacturing requirements** of safety and performance, some of which are relevant to each medical device. …"

- "… These are grouped as:
  - Chemical, physical and biological properties
  - Infection and microbial contamination
  - Manufacturing and environmental properties
  - Devices with a diagnostic or measuring function
  - Protection against radiation
  - Requirements for medical devices connected to or equipped with an energy source
  - Protection against mechanical risks …

“Part 1”, “Part 2” Standards

- Part 1 – Generically applied to all devices
  - IEC 60601.1 - Medical Electrical equipment – General requirements for safety – **Parent Standard**
  - IEC 60601.1.2 - Medical Electrical equipment – General requirements for safety – **Collateral Standard**: Electromagnetic compatibility – requirements and tests
  - IEC 60601.1.3 - Medical Electrical equipment – General requirements for safety – **Collateral Standard**: Requirements for radiation protection in diagnostic X-ray equipment
  - ……. Plus several others
- These apply to all medical electrical equipment

“Part 1”, “Part 2” Standards

- Part 2 Standards are device Specific
  - IEC 60601.2.1– Medical electrical equipment – **Particular requirements for safety** - Electron accelerators in the range 1 MeV to 50 MeV
  - IEC 60601.2.2– Medical electrical equipment – **Particular requirements for safety** – High frequency surgical equipment
  - IEC 60601.2.2 – Medical electrical equipment – **Particular requirements for safety** – Cardiac defibrillators and cardiac defibrillator-monitors
  - IEC 60601.2.3: – Medical electrical equipment – **Particular requirements for safety** – High voltage generators of diagnostic X-ray generators
  - ..... >> 50 other Part 2’s
- These apply to particular types of equipment

“Part 1”, “Part 2” Standards

- Note also joint ISO/IEC standards ……
- For example –
  - IEC 80601-2-30 - Medical electrical equipment — Part 2-30: Particular requirements for basic safety and essential performance of automated non-invasive sphygmomanometers
  - ISO 80601-2-61 - Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment

Biocompatibility and Standards

8. Chemical, physical and biological properties

8.1 The medical devices shall be designed and manufactured in such a way as to ensure the characteristics and performance requirements referred to in Clauses 1 to 6 of the 'General Requirements' are met.

Particular attention shall be paid to:

- the choice of materials used, particularly as regards toxicity and, where appropriate, flammability,
- the chemical and physical properties of the material used,
- the compatibility between the materials used and biological tissues, cells, body fluids, and specimens, taking account of the intended purpose of the medical device,
- the choice of materials used shall reflect, where appropriate, matters such as hardness, wear and fatigue strength.

* ASEAN Medical Device Directive

Biocompatibility of Materials

- ISO 10993.1 – Biological evaluation of medical devices – Part 1: Evaluation and testing
  - ISO 10993.3 – Biological evaluation of medical devices – Part 3: Tests for genotoxicity, carcenogenicity, and reproductive toxicity
  - ISO 10993.6 – Biological evaluation of medical devices – Part 6: tests for local effects after implantation
  - ISO 10993.11 – Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
  - ..... ~ 15 in total

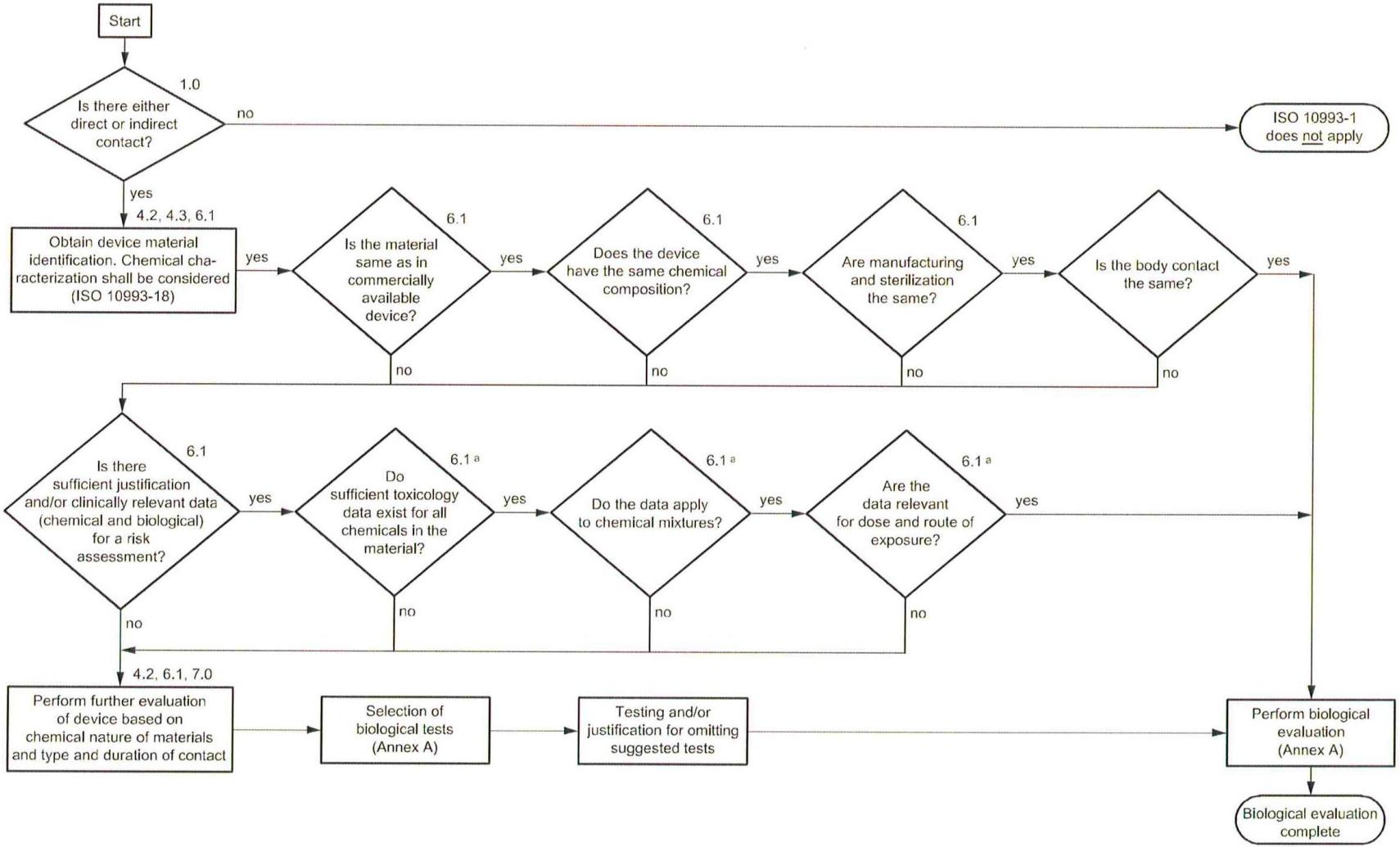

Start
1.0
Is there either direct or indirect contact?
no
ISO 10993-1 does not apply
yes
4.2, 4.3, 6.1
Obtain device material identification. Chemical characterization shall be considered (ISO 10993-18)
yes
6.1
Is the material same as in commercially available device?
yes
6.1
Does the device have the same chemical composition?
yes
6.1
Are manufacturing and sterilization the same?
yes
Is the body contact the same?
yes
no
no
no
no
6.1
Is there sufficient justification and/or clinically relevant data (chemical and biological) for a risk assessment?
yes
6.1 a
Do sufficient toxicology data exist for all chemicals in the material?
yes
6.1 a
Do the data apply to chemical mixtures?
yes
6.1 a
Are the data relevant for dose and route of exposure?
yes
no
no
no
no
4.2, 6.1, 7.0
Perform further evaluation of device based on chemical nature of materials and type and duration of contact
Selection of biological tests (Annex A)
Testing and/or justification for omitting suggested tests
Perform biological evaluation (Annex A)
Biological evaluation complete

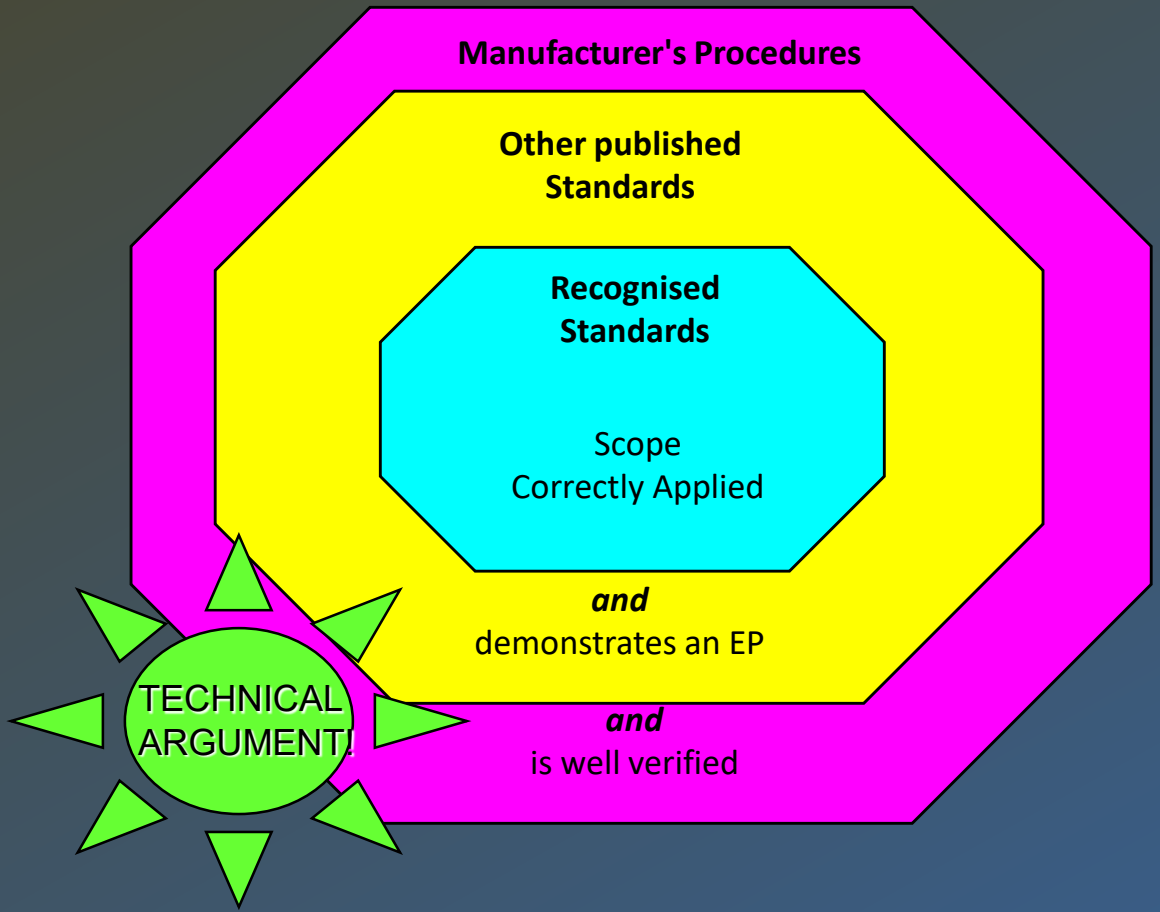
Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (⩽ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

Demonstrating conformity

- **Presumption of Conformity**
  - Compliance with processes, and subsequent application of relevant testing provides a presumption of conformity to the applicable Essential Principle(s)


Manufacturer's Procedures
Other published Standards
Recognised Standards
Scope
Correctly Applied
and
demonstrates an EP
and
is well verified
TECHNICAL ARGUMENT!

In Summary

- Essential Principles form the foundation of harmonized global regulatory model

- They
  - are comprehensive in scope
  - cover safety and performance
  - define design requirements
  - do not define methods of achieving, demonstrating, or documenting conformity
  - are most often addressed by using international standards

In summary

- The manufacturer must apply all general principles and all relevant specific principles
- They are flexible to accommodate advances in the state of the art and new medical devices / technologies / intended uses
- They recognize risks and benefits associated with medical devices
- They are founded on risk management principles
- They are intimately linked to a manufacturer's quality system for design, manufacture, and risk management

But……

- They have their origins back in the early 90's
- Technologies and the practice of medicine has moved on…….

Essential Principles

- Essential Principles lay down the necessary elements for protecting the public interest e.g. health, safety and environmental issues i.e. all that is necessary to achieve objective of regulatory AMDD. (Article 3)
- They define the results to be attained or the hazards to be dealt with, they do not specify the technical solutions to be adopted
- They are not based on technical requirements and are not affected by technological progress or innovation. Consequently, they are not subject to regular revision.
- They are mandatory when applicable. Rationales for non-compliance are not an option

- The EP's originated from the EU ER's……93/42/EEC and 9/385/EEC
  - 13 EP's in MDD
  - 16 EP's in AIMD

- Now –EU Medical Device Regulations 2017
  - 23 General Safety and Performance Requirements

New considerations from Annex I

- medicinal substances (and substances absorbed or locally dispersed);
- devices incorporating materials of biological origin
- substances of concern
  - Nano particles, latex, phthalates……..
- labelling requirements
- cybersecurity

- Other key areas of impact in the MDR outside Annex I include:

  - clinical data and evaluation requirements
  - reclassification of some device types
  - post-market requirements

Perhaps now is the time to revisit the EP's ……

- But who …….
  - IMDRF
  - AHWP
  - Individual regulators

Questions, comments, thoughts ……

Michael Flood BE FIEAust CPEng(Biomedical) NER
Locus Consulting P/L
AUSTRALIA

mike@locusconsulting.net.au
T: +61 (0)2 6112 8325
M: +61 (0)40 1147 605