Asia-Pacific
Economic Cooperation

Report on APEC-Funded Seminars on Harmonization of Medical Device Regulations

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Annex: Presentation Slides, Kuala Lumpur, Malaysia March 5 – 7, 2008

Life Sciences Innovation Forum
APEC Committee on Trade and Investment

August 2009

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4TH Asia-Pacific Economic Cooperation (APEC)-Funded Seminar on Harmonization of Medical Device Regulations, - Presentation Slides

1_APEC KL - SG1 Classification-John Brennan.pdf (size: 128KB)
1_APEC_SG3_Training Overview KL 2008-Gunter Frey-Hideki Asai.pdf (size: 62KB)
2008 KL- GHTF SG5 final.pdf (size: 160KB)
2008-03-05 Overview of GHTF SG2 and NCAR - JG -PA V3.pdf (size: 433KB)
2_APEC AHWP KL Mar 08 Definition Manufacturer Gropp.pdf (size: 102KB)
2_APEC KL - SG1 Role of Standards-John Brennan.pdf (size: 104KB)
2_APEC_SG3_Role Members Documents KL 2008-Gunter Frey.pdf (size: 80KB)
3_APEC KL - SG1 Labelling-John Brennan.pdf (size: 83KB)
3_APEC KL Mar 08 SG1 Essential Principles Gropp-M.Gropp.pdf (size: 492KB)
3_APEC_SG3_QMS History and Evolution KL 2008-Gunter Frey.pdf (size: 91KB)
4_APEC_SG3_ISO13485 Introduction KL 2008-Gunter Frey-Hideki Asai.pdf (size: 898KB)
5_APEC_SG3_RM Principles within a QMS KL 2008-Gunter Frey-Hideki Asai.pdf (size: 192KB)
6_APEC_SG3_Process Validation Training KL 2008 -Gunter Frey.pdf (size: 206KB)
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APEC KL - Definition-John Brennan.pdf (size: 78KB)
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APEC KL March 2008 SG 4 Summary Final-Tim Missios.pdf (size: 372KB)
CER Format.pdf (size: 27KB)
GHTF-K-Larry Mar 08-New.pdf (size: 270KB)
General overview of SG1 March 2008 (2) G Michaud.pdf (size: 137KB)
General overview of SG1 March 2008 (2)on behalf G Michaud.pdf (size: 137KB)
IVD Medical Device V2.pdf (size: 227KB)
Medical Devices - Integrity in the Supply Chain - Shelley Tang.pdf (size: 83KB)
THE ROLES & RESPONSIBILITIES IN THE SUPPLY CHAIN V1.pdf (size: 61KB)

Principles of Medical Devices Classification

GHTF/SG1/N15:2006

John Brennan
European Commission

Principles of Medical Devices Classification

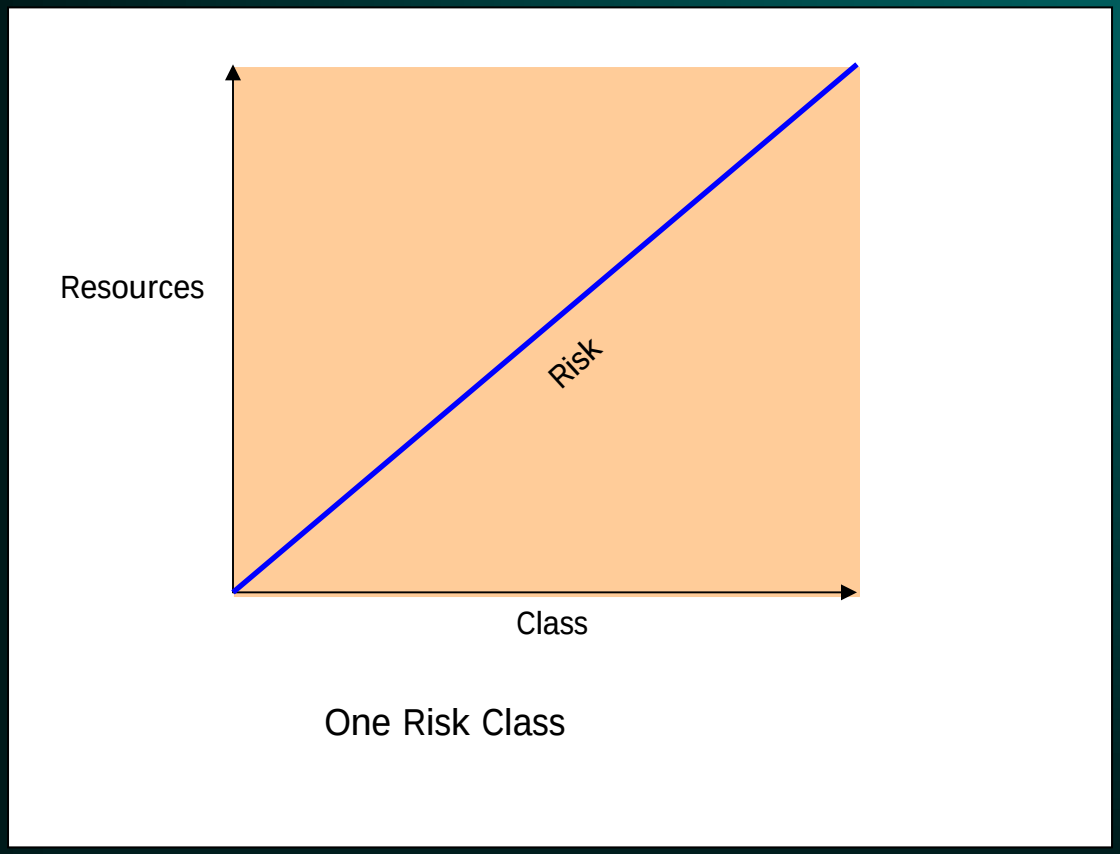
Why Classify?

Answer:

- **Economic and effective control of devices**
- **Resources in line with Risk**

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
- Factors
- The Rules
- Who Classifies?
- Common Errors
- Changes to Classification

Principles of Medical Devices Classification



- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
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- The Rules
- Who Classifies?
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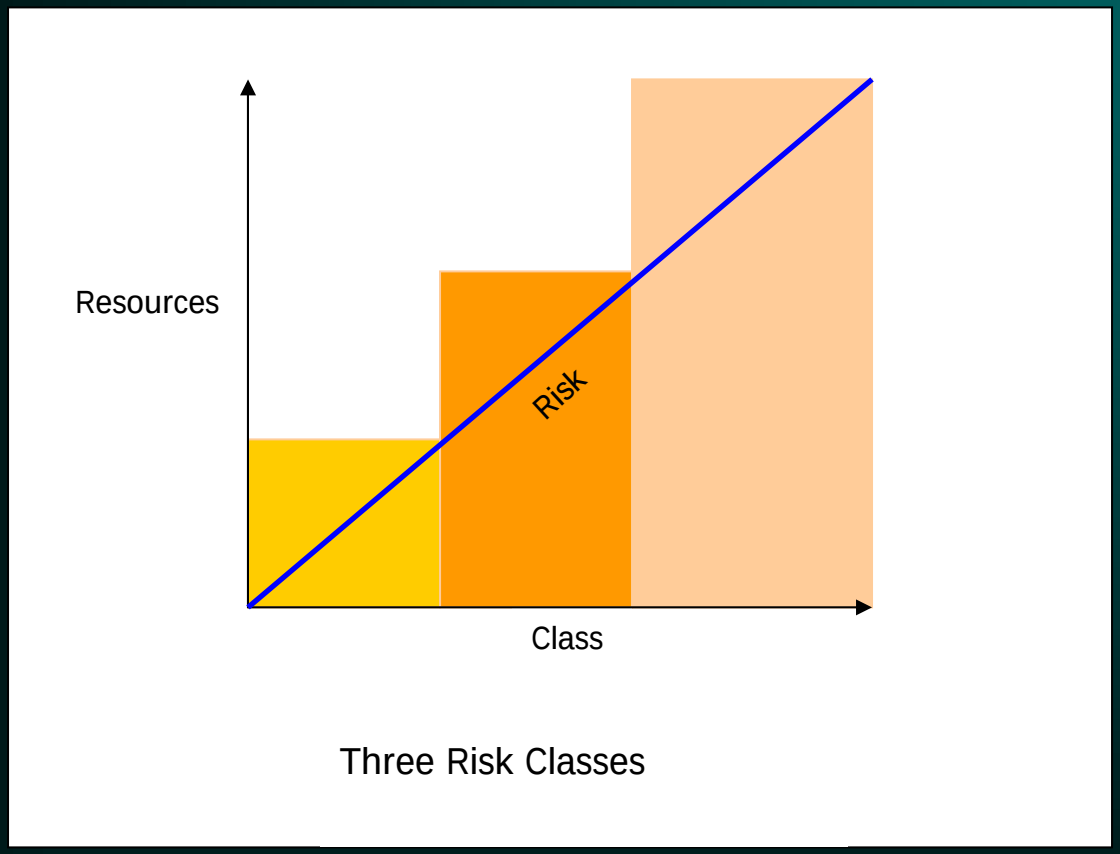
- Changes to Classification

Principles of Medical Devices Classification

Two Risk Classes

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
- Factors
- The Rules
- Who Classifies?
- Common Errors
- Changes to Classification

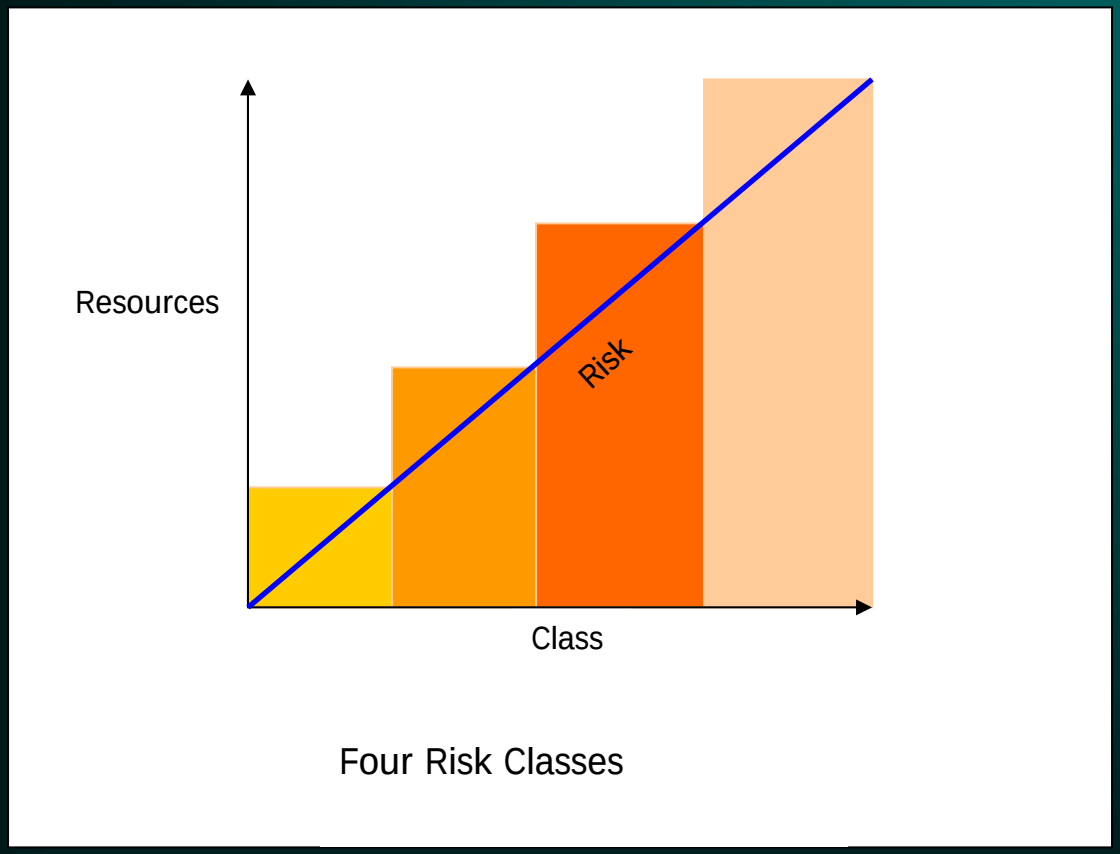
Principles of Medical Devices Classification



Three Risk Classes

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
- Factors
- The Rules
- Who Classifies?
- Common Errors
- Changes to Classification

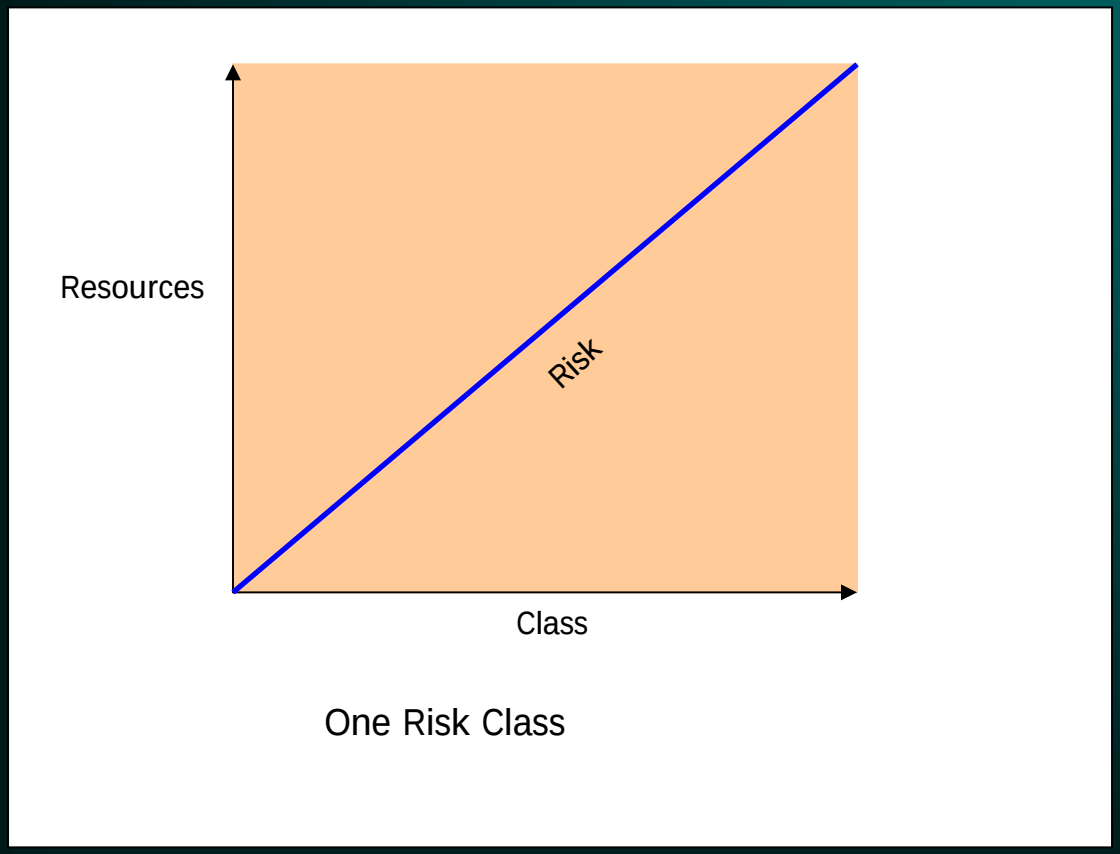
Principles of Medical Devices Classification



Four Risk Classes

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
- Factors
- The Rules
- Who Classifies?
- Common Errors
- Changes to Classification

Principles of Medical Devices Classification



- Why Classify?
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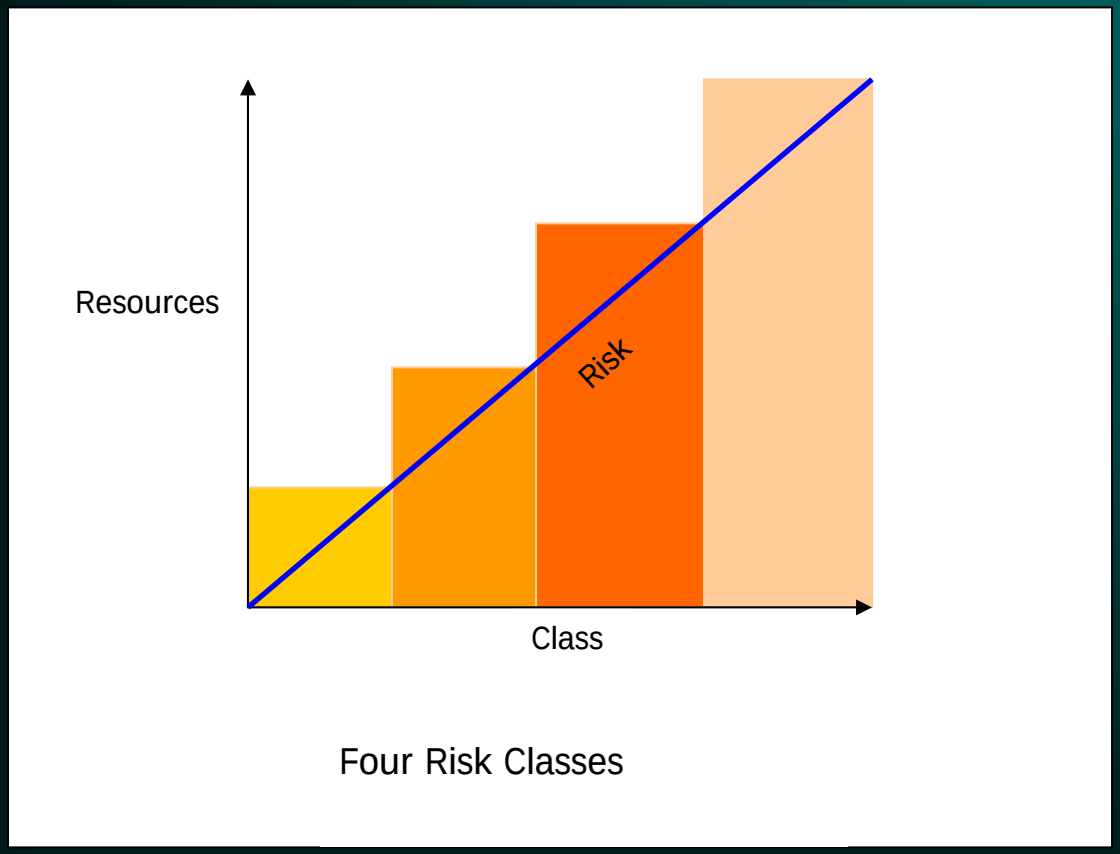
Principles of Medical Devices Classification



- Why Classify?
- Rationale Used
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- Recommendations
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- Who Classifies?
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- Changes to Classification

Principles of Medical Devices Classification

Why Classify?

Why four classes?

Answer:

Based on experience of GHTF Founding Members, this is sufficient to accommodate all medical devices and allows an efficient and graduated system of conformity assessment controls.

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
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- The Rules
- Who Classifies?
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Principles of Medical Devices Classification

Rationale Used

What makes a product fall in a certain class and not another?

Answer:

Risk to patients, users and other persons

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
- Recommendations
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Principles of Medical Devices Classification

Risk to patients, users and other persons

Which in turn depends on:

- Intended purpose
- Risk management applied
- Intended Users
- Mode of Operation or Technologies

- (Also Novel Devices)

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
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- Who Classifies?
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- Changes to Classification

Principles of Medical Devices Classification

Risk Class and Technical Documentation

Common Misconception:

The lower the risk class the less technical documentation is needed

Reality:

All the Essential Principles apply no matter the risk class; it is the characteristics of the device that determine the depth and detail of the technical documentation

- Why Classify?
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Principles of Medical Devices Classification

Risk Class and Technical Documentation

Common Misconception:

The lower the risk class the less technical documentation is needed

Reality:

All the Essential Principles apply no matter the risk class; it is the characteristics of the device that determine the depth and detail of the technical documentation

Including Clinical Evidence!!!!

- Why Classify?
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Principles of Medical Devices Classification

Recommendations

Primary Recommendations (The logic of the system)

- Strive to be global
- 4 classes
- Rules should lead to consistency between manufacturers and regulators
- Clear
- Robust to technology
- Manufacturers should document their determination of the risk classification and under which rule or rules
- Final determinations that deviate should be balanced against disharmonization

Principles of Medical Devices Classification

Factors

- Duration and nature of contact
- Delivering a Medicinal Product or Energy
- Biological Effects
- Multiple Rules Applying – highest risk class applies
- Discrete Classification – separate application of rules
- Combinations – Change in intended use; Not yet approved devices
- Accessories
- Software
- Subject to Change

Principles of Medical Devices Classification

The Rules

Currently 16 rules in 4 Sections

- Non-invasive Devices
- Invasive Devices
- Active Devices
- Additional Rules

- Why Classify?
- Rationale Used
- Risk Class and Technical Documentation
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- The Rules
- Who Classifies?
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- Changes to Classification

Principles of Medical Devices Classification

The Rules

Additional Rules

- Medicinal Products
- Animal or Human Tissues
- Disinfectants
- Contraceptives

- Why Classify?
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Principles of Medical Devices Classification

Who Classifies?

Initially classification by the Manufacturer (Documented)

followed by

Final, confirmatory, classification by the Regulatory Authority

- Why Classify?
- Rationale Used
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Principles of Medical Devices Classification

Common Errors

- Not a device
- Stop at first rule that fits
- Ignore sub-paragraphs to the rules (unless...)
- Not realize that one of the 'Additional Rules' applies
- Misinterpret definitions, e.g. degrees of invasiveness

Principles of Medical Devices Classification

Changes to Classification

Jurisdictions may have to adjust their classification

- Post-market Experience
- Historical Knowledge
- National Rules

And GHTF itself will review this document

- Why Classify?
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Principles of Medical Devices Classification

Thank You For Listening

- Why Classify?
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GHTF SG3 Training Overview

4th APEC-Funded Seminar on Harmonization of Medical Device Regulation

Kuala Lumpur

March 5-7, 2008

Gunter Frey
Hideki Asai

GHTF SG3 Training Overview

1. **GHTF SG3 – Role, Members, Documents**
2. **Quality Management Systems: History and Evolution**
3. **ISO13485:2003 - An Overview**
4. **Risk Management Principles and Activities Within a Quality Management System**
5. **Process Validation**

Definition of the Terms “Manufacturer”, “Authorised Representative”, “Distributor”, and “Importer”

4th APEC-Funded Seminar on
Harmonization of Medical Device Regulation

The Role of Regulators, Industry, and Distributors in Harmonization of Medical Device Regulation in the Asia/Pacific Region

Kuala Lumpur, 6 March 2008

M. Gropp, Medtronic, Inc., Minneapolis, USA

Introduction

- Basic document in GHTF “global regulatory model”
- Who is deemed a “manufacturer”, “authorised representative”, “distributor”, or “importer” and why?
- Foundation for regulation
  - “What” is regulated?
  - “Who” is regulated?
  - “How” are they regulated?
- Determines jurisdiction, roles and responsibilities

Draft GHTF guidance document

- Early stage drafting in Study Group 1
  - Consultation with SG-3 and SG-4
- Not yet available on GHTF website
- This preview presentation based on current Study Group draft
  - ***Note:*** Document subject to change, perhaps significantly
- Comments to Study Group 1 welcome

Rationale

- Term “manufacturer” appears in many GHTF documents – but is undefined
- Term is associated with various obligations and responsibilities
- Consistent, harmonised definition would support convergence of regulatory systems
- Benefits to regulatory authorities and parties responsible for making and/or placing medical devices onto market

Purpose

- To provide harmonised definitions of terms “manufacturer”, “authorised representative”, “distributor” and “importer”
- To allow regulatory authority to establish identity of person who takes responsibility for ensuring the finished medical device meets relevant regulatory requirement within its jurisdiction
- Guidance for regulatory authorities, conformity assessment bodies, and industry
- Improve clarity of existing GHTF guidance

Scope

- Applies to products that fall within GHTF definition of “medical device”, including IVDs

Definitions – Manufacturer

- Any natural or legal person …
  - “Person” includes legal entities such as a corporation, a partnership, or an association

Definitions – Manufacturer

- Any natural or legal person who designs and/or manufactures …

Definitions – Manufacturer

- Any natural or legal person who designs and/or manufactures a medical device …
  - GHTF definition of “medical device”

Definitions – Manufacturer

- Any natural or legal person who designs and/or manufactures a medical device with the intention of making the finished medical device available for use, …
  - Intention – need not yet have made device available for use
  - “Finished device” intended to exclude subcontractors, contract sterilisers, etc.

Definitions – Manufacturer

- Any natural or legal person who designs and/or manufactures a medical device with the intention of making the finished medical device available for use, under his name; …
  - Importance of labelling in determining who is “manufacturer”

Definitions – Manufacturer

- Any natural or legal person who designs and/or manufactures a medical device with the intention of making the finished medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by a third party(ies)

Definitions – Manufacturer

- This natural or legal person has the ultimate responsibility for ensuring compliance with all applicable regulatory requirements for the medical device in the countries or jurisdictions where it is intended to be made available or sold

- Manufacturer’s responsibilities described in other GHTF guidance documents – include pre- and post-marketing requirements (e.g., vigilance reporting and notification of field safety corrective actions)

Definitions – Manufacturer

- Design and/or manufacture may include
  - Specification development, production, fabrication, assembly, processing, packaging, repackaging, labelling, relabelling, sterilisation, installation, or remanufacturing; and/or
  - Assembly, packaging, processing and/or labelling of one or more finished products

Definitions – Manufacturer

- Any person who assembles or adapts a device(s) that has already been supplied by another person for an individual patient, in accordance with the instructions for use, is not the manufacturer, provided the assembly or adaptation does not change the intended use of the device(s)

Definitions – Manufacturer

- Any person who changes the intended use of, or modifies, a finished medical device in a way that may affect safety or performance, without acting on behalf of the original manufacturer and who makes it available for use under his own name should be considered the manufacturer of the modified medical device

Definitions – Manufacturer

- To the extent an accessory is subject to regulatory requirements (see definition of “medical device”), the person responsible for the design and/or manufacture of that accessory is deemed to be a manufacturer

Definitions – Authorised Representative

- Any natural or legal person established within a country or jurisdiction who has received a mandate from the manufacturer to act on his behalf for specified tasks with regard to the latter’s obligations under that country or jurisdiction’s legislation

Definitions – Distributor

- Any natural or legal person in the supply chain who, on his own behalf, furthers the availability of a medical device to the end user
  - In some circumstances, more than one distributor may be involved in this process
  - A distributor who indicates his own address and contact details on the medical device or its packaging, but does not otherwise repackage or relabel the device or its packaging, and does not modify the medical device in a way that many affect safety, performance, or intended use, is not considered a manufacturer

Definitions – Importer

- Any natural or legal person in the supply chain who first makes a medical device, manufactured in another jurisdiction, available in a country or jurisdiction where it is to be marketed
  - An importer does not repackage or relabel the device or device package, and does not transform or modify a medical device in a way that may affect safety, performance or intended use

Guidance

- A single party may fulfil one or more of these roles
  - e.g., a manufacturer may not only distribute the products it manufacturers but it may also act as a distributor or importer of devices from a different manufacturer

Questions?

Role of Standards in the Assessment of Medical Devices

GHTF/SG1/N012:2000

(and updates due in 2008 version)

John Brennan
European Commission

Role of Standards in the Assessment of Medical Devices

Which Standards?

Answer:

International Consensus Standards

- Basic (horizontal)
- Group (semi-horizontal)
- Product (vertical)

International standards represent global opinions of experts from all interested parties, including industry, regulators, users and others

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
- Using Superseded Versions
- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

What is their Role?

Answer:

- International consensus standards are a tool for harmonization to assure the quality safety and performance of medical devices as set out in the Essential Principles
- International consensus standards can set out the technical specifications that an authority can 'Recognise' as meeting one or more Essential Principles
- Manufacturers who meet 'Recognised Standards' can benefit from a 'Presumption of Conformity' to the applicable Essential Principles

Role of Standards in the Assessment of Medical Devices

Recognised Standards

In order for a manufacturer to know which standards to be used, it should be 'Recognised'

Authorities should provide for:

- Recognition Mechanism
- Identify the Standards (version and date)
- Periodic Review
- Official Publication of Lists
- Voluntary (exceeds standard, particular product characteristics or innovation)

- Which Standards?
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Role of Standards in the Assessment of Medical Devices

2008 Updates

- Extend Scope to include *in vitro* diagnostic medical devices
- Provide guidance on use of recognised standards that have been revised or replaced

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
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- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Revision to Standards

Why are standards revised?

- Standard no longer deemed to meet the Essential Principle
- Essential Principles change
- Technological progress necessitates an update to the standard

So revision is a normal activity

- Which Standards?
- What is their Role?
- Recognised Standards
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Role of Standards in the Assessment of Medical Devices

Change of Status

So revision is a normal activity, but revision has an effect on status

So does post-market experience of device safety

- An authority may cease to recognise a standard due to safety concerns identified trough post-market activities or through user experience (and request a revision or alternative solution)
- And in all cases the authority will have to submit the new revision to the recognition mechanism, with the replacement of the old revision

- Which Standards?
- What is their Role?
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Role of Standards in the Assessment of Medical Devices

Change of Status

Depending on the reason for ceasing recognition of a standard the authority should:

- set a date of removal of presumption of conformity
- which could be immediate for safety concerns
- for reasons other than safety, this date should allow manufacturers a sufficient 'Transition Period' to adapt

Role of Standards in the Assessment of Medical Devices

Use during Transition

The world doesn't stop for standards.
What do I do with the devices I have in the design pipeline and on my factory floor?

Which standard do I use, the old or the new?

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
- Using Superseded Versions
- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Use during Transition

Answer:

During the Transition Period – Both

After the Transition Period – Only the new

- Which Standards?
- What is their Role?
- Recognised Standards
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Role of Standards in the Assessment of Medical Devices

Use during Transition

Answer:

During the Transition Period – Both

After the Transition Period – Only the new

If you want to maintain the benefit of presumption of conformity

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
- Using Superseded Versions
- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Using Superseded Versions

You can use superseded versions but you do not benefit from the presumption of conformity

You still have to meet the Essential Principles and you should justify your decision through a documented risk assessment and take any risk mitigation action as appropriate

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
- Using Superseded Versions
- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Using Superseded Versions

What about devices I've already produced and that are out there in the market?

Devices already in the supply chain or with the user prior the transition period (i.e. designed and manufactured to the superseded version) are not affected by the recognition of the new standard and can continue to be supplied and used...

...unless there are safety implications in which case the manufacturer should implement a risk mitigation strategy and take appropriate action to address these safety concerns

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
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- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Alternatives to Standards

Standards are voluntary – alternatives are allowed

Manufacturers may use “non-recognised” standards, in whole or in part, or other methods.

- Which Standards?
- What is their Role?
- Recognised Standards
- 2008 Updates
- Revision to Standards
- Change to Status
- Use during Transition
- Using Superseded Versions
- Alternatives to Standards

Role of Standards in the Assessment of Medical Devices

Alternatives to Standards

Alternative means of demonstrating conformity with the Essential Principles may include:

- national and international standards that have not been given the status of a "recognised standard" by the Regulatory Authority;
- industry agreed methods;
- internal manufacturer standard operating procedures developed by an individual manufacturer;
- other sources that describe the current state of technology and practice related to performance, material, design, methods, processes or practices.

Role of Standards in the Assessment of Medical Devices

Alternatives to Standards

The acceptability of such other solutions should be justified and may be subject to review by the RA/CAB, as appropriate.

- Which Standards?
- What is their Role?
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Role of Standards in the Assessment of Medical Devices

Thank You For Listening

- Which Standards?
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GHTF Study Group 3
Role, Members, Documents

4th APEC-Funded Seminar on
Harmonization of Medical Device Regulation
Kuala Lumpur
March 5-7, 2008

Gunter Frey
Vice Chair SG3

Role of Study Group 3

- "SG3 is responsible for the task of examining existing quality system requirements in countries having developed device regulatory systems and identifying areas suitable for harmonization."
- www.ghtf.org/sg3/sg3.htm

Members (2008)

Australia

- Mr Ken Nicol — MIAA/St. Jude
- Mr Keith Smith — TGA/MAB

Canada

- Mr Egan Cobbold — HC/MDB (Chair of SG3)
- Mr Jan Noupbaev — MEDEC/Medtronic Can.

European Union

- Mr Carlos Arglebe — COCIR/Siemens
- Mr Victor Dorman-Smith — EUCOMED
- Mr Dirk Wetzels* — EU/BfArM (Germany)

Japan

- Mr Hideki Asai — JFMDA/Hitachi
- Mr Munehiro Nakamura — JFMDA/Kaneka
- Mr Shinichi Takae — MHLW

United States of America

- Ms Kimberly Trautman — FDA
- Mr Gunter Frey — NEMA/GE Healthcare (Vice-Chair/Sec of SG3)
- Mr Ken Kopesky — AdvaMed/Medtronic

SG3 Documents – the present

Since 1992, the study group has prepared and published four guidance documents. Two are “final” and two have been “archived” because their contents were transferred to ISO/TR 14969:2004

Final Documents

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

SG3/N15R8/2005 Implementation of Risk Management Principles and Activities Within a Quality Management System

Archived Documents

GHTF.SG3.N99-8 Guidance On Quality Systems For The Design And Manufacture Of Medical Devices

GHTF.SG3.N99-9 Design Control Guidance For Medical Device Manufacturers

SG3 Documents – the future

Study Group 3 is currently working on a new guidance document that is intended to provide harmonized guidance for manufacturers on the control of products and services obtained from suppliers.

"SG3(WD)N17 Quality management system – Medical devices- Guidance on the control of products and services from suppliers". Expect to have a draft out for public comment by early 2008.

In next 4 to 5 years our plan is to develop 2 new guidance documents on "characterizing the significance of quality management system deficiencies", and "corrective and preventive action (CAPA) principles and activities."

SG3 Documents - partnership

Since 1992, the study group has worked in partnership with ISO TC 210/WG1 to develop four ISO documents:

ISO 13485:1996 Quality systems-Medical devices-Particular requirements for the application of ISO 9001

ISO 13488:1996 Quality systems-Medical devices-Particular requirements for the application of ISO 9002

ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purpose

ISO/TR 14969:2004 Medical devices — Quality management systems — Guidance on the application of ISO 13485:2003

Labelling for Medical Devices

GHTF/SG1/N43:2005

John Brennan
European Commission

Labelling for Medical Devices

Definition of Labelling

Written, printed or graphic matter affixed to a medical device or any of its containers or wrappers, or, accompanying a medical device, related to identification, technical description, and use of the medical device, but excluding shipping documents.

Note: Some regional and national regulations refer to 'Labelling' as 'Information supplied by the manufacturer' (Source – ISO 13485)

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Importance of Labelling – Why did GHTF look at this?

Safety

Information to the patient or user is critical to safe use

Promote Trade

Different labelling requirements in different jurisdictions can be a barrier to trade

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Safety

Information to the patient or user is critical to safe use:

"Labelling serves to communicate safety and performance related information to users of medical devices and/or patients as well as to identify individual devices."

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
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Labelling for Medical Devices

Promote Trade

Different labelling requirements in different jurisdictions can be a barrier to trade:

"Consistent worldwide labelling requirements would offer significant benefits to the manufacturer, user and/or patient, and to Regulatory Authorities."

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Purpose of Labelling

Clearly inform the user of:

- identity of the device (which device is it?)
- its intended use/purpose
- how it should be used, maintained and stored
- any residual risks, warnings or contra-indications

- Definition of Labelling
- Importance of Labelling
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Labelling for Medical Devices

Purpose of Labelling

Clearly inform the user of:

- identity of the device (which device is it?)
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- how it should be used, maintained and stored
- any residual risks, warnings or contra-indications

SAFETY

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Purpose of Labelling

Whilst also promoting:

- labelling commensurate with the technical knowledge, experience, education or training of intended users
- use of symbols
- the avoidance of prescriptive country-specific requirements for labelling text, content, or the format of labels or labelling that offer no user or patient benefit

Labelling for Medical Devices

Purpose of Labelling

Whilst also promoting:

- labelling commensurate with the technical knowledge, experience, education or training of intended users
- use of symbols
- the avoidance of prescriptive country-specific requirements for labelling text, content, or the format of labels or labelling that offer no user or patient benefit

TRADE (and SAFETY)

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

General Principles

So in GHTF we set out some principles:

- Where to put the labeling/Information
- Single IFU if appropriate
- Medium, format, content readability and location
- Labelling of Simple devices
- Note on media (paper vs electronic)
- Residual risks
- Eliminate country specific labeling
- Symbols

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Label Data

And then we set out the data that achieves the safety aim while promoting trade:

- Identity: Name, address, lot number, etc.
- How to use the device
- Warnings, precautions and contra-indications
- Sterility
- Implantable Risks
- Use in combination
- Disposal
- Etc.
- Etc.

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Language

Labelling should be:

- Appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s)
- Readily understood by the intended user
- Where appropriate, supplemented with drawings and diagrams
- Where the meaning of the symbol is not obvious to the device user, e.g. for a lay-user or for a newly introduced symbol, an explanation should be provided
- Provided that safe and correct use of the device is ensured, a Regulatory Authority may authorise labelling to be in one or more language(s) other than its national language(s)

Labelling for Medical Devices

National Variation

2.1 Rationale

Consistent worldwide labelling requirements would offer significant benefits to the manufacturer, user and/or patient, and to Regulatory Authorities. Eliminating or reducing differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

2.2 Purpose

"...the avoidance of prescriptive country-specific requirements for labelling text, content, or the format of labels or labelling that offer no user or patient benefit.

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Labelling for Medical Devices

Thank You For Listening

- Definition of Labelling
- Importance of Labelling
- Purpose of Labelling
- General Principles
- Label Data
- Language
- National Variation

Essential Principles of Safety and Performance of Medical Devices

4th APEC-Funded Seminar on
Harmonization of Medical Device Regulation

The Role of Regulators, Industry, and Distributors in Harmonization of Medical Device Regulation in the Asia/Pacific Region

Kuala Lumpur, 6 March 2008

M. Gropp, Medtronic, Inc., Minneapolis, USA

Only medical devices that are safe and perform as intended should be allowed in the market

- ☐ Agree
- ☐ Disagree

Presentation overview

- Introduction
- Purpose
- Overview of main points of Essential Principles guidance document

GHTF guidance documents

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GHTF

1992 - 2008

Global Harmonization Task Force

Working Towards Harmonization in Medical Device Regulation

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GHTF > Home

Welcome to the Global Harmonization Task Force Website

The Global Harmonization Task Force was conceived in 1992 in an effort to achieve greater uniformity between national medical device regulatory systems. This is being done with two aims in mind: enhancing patient safety and increasing access to safe, effective and clinically beneficial medical technologies around the world.

A partnership between regulatory authorities and regulated industry, the GHTF is comprised of five Founding Members: European Union, United States, Canada, Australia and Japan. The chairmanship is rotated among the Founding Members and presently resides with the United States.

Quick Links

- Annual Conference
- Event Calendar
- New Policy
- Latest Guidance Documents
- Documents in Other Languages *Coming Soon
- Training Opportunities

In the News

- SG2 Participants (21 February 2008)
- SG2 Meeting Minutes (21 February 2008)
- GHTF/APEC Training - 5-7 March 2008 - Kuala Lumpur, Malaysia (14 January 2008)
- SG4 Participants (10 January 2008)
- Steering Committee Chair Page and Member List (21 November 2007)
- 2007-2008 GHTF Calendar (20 December 2007)

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GHTF > Study Groups > Study Group 1 (SG1) > SG1 - Final Documents

SG1 - Final Documents

Title	Description	Posted Date	Size	Comments To
SG1-N15:2006 PDF Word	Principles of Medical Devices Classification	31 August 2006	27 pages	
SG1-N40:2006 PDF Word	Principles of Conformity Assessment for Medical Devices	31 August 2006	16 pages	
SG1-N43:2005 PDF	Labelling for Medical Devices	29 August 2005	10 pages	
SG1-N29R16:2005 PDF	Information Document Concerning the Definition of the Term "Medical Device"	21 July 2005	6 pages	
SG1-N41R9:2005 PDF	Essential Principles of Safety & Performance of Medical Devices	21 July 2005	6 pages	
SG1-N012R10 PDF Word	Role of Standards in the Assessment of Medical Devices	15 March 2000 *Re-posted: 23 October 2000	10 pages, 50Kb-PDF 73Kb-Word	

*Reposted dates indicate when the document was reposted with a standard format cover sheet.

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GHTF/SG1/N41R9:2005

GHTF

FINAL DOCUMENT

Title: Essential Principles of Safety and Performance of Medical Devices

Authoring Group: GHTF Study Group 1

Endorsed by: The Global Harmonization Task Force

Date: May 20, 2005

Abraao Carvalho, GHTF Chair

This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide non-binding guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

There are no restrictions on the reproduction, distribution or use of this document, however, incorporation of this document, in part or in whole, into any other document, or its translation into languages other than English, does not convey or represent an endorsement of any kind by the Global Harmonization Task Force.

Document history

"The GHTF has identified as a priority the need to harmonize essential safety and performance criteria for a medical device that allow the manufacturer to demonstrate its product is suitable for its intended use.

This goal was achieved through the publication of guidance on the subject entitled *Essential Principles of Safety and Performance of Medical Devices* (SG1/N020 of June 30, 1999) that applied to the majority of medical devices but not to *in vitro* diagnostic devices. …"

Document history

"…. This current document supersedes that earlier one. The major difference between them is the expanded scope; this document now includes medical devices for the *in vitro* examination of specimens derived from the human body."

Rationale

"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. ..."

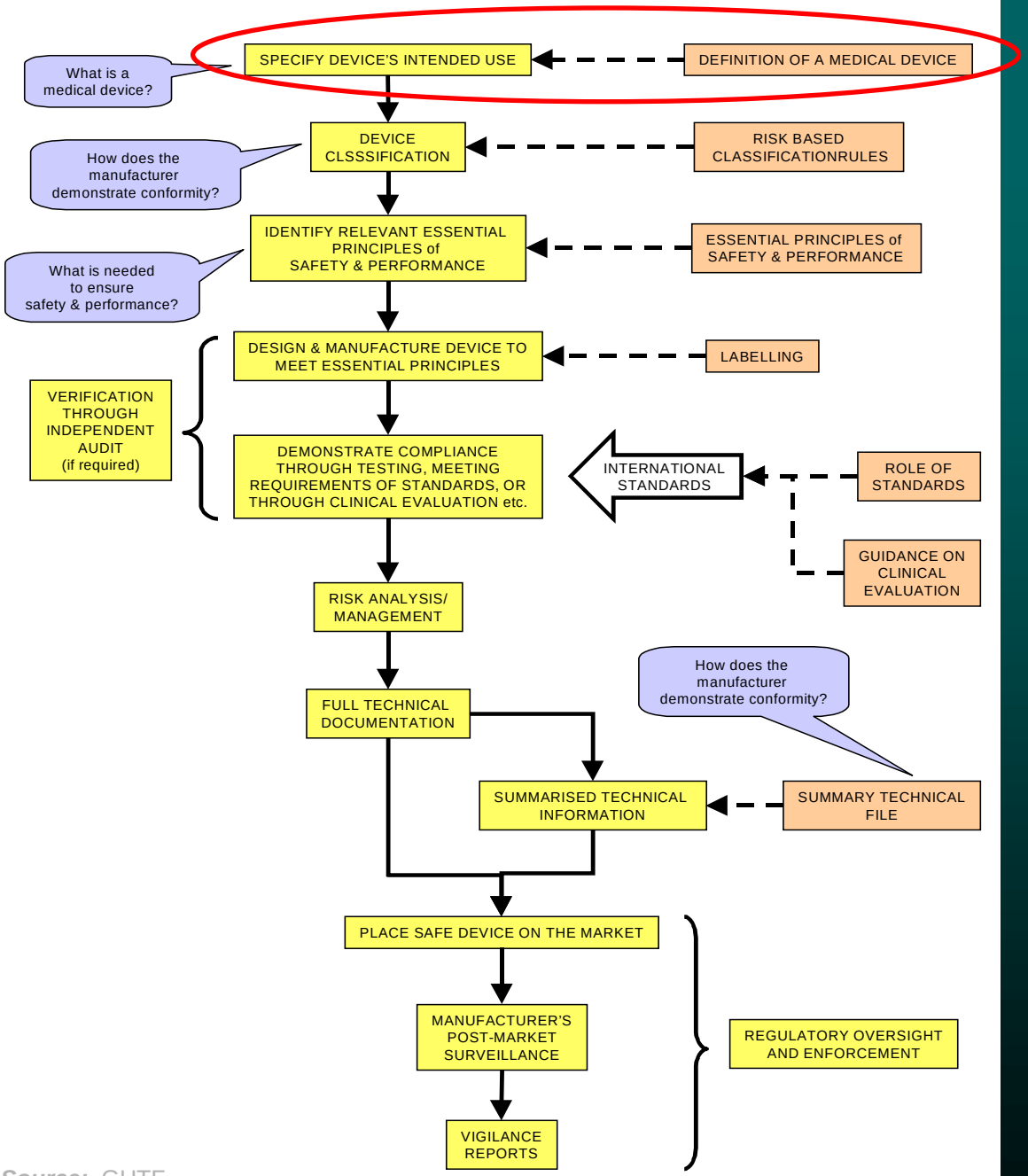
Rationale

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

Scope

"This document applies to all products that fall within the definition of a medical device that appears within the GHTF document *Information Document Concerning the Definition of the Term "Medical Device"*, including those used for the *in vitro* examination of specimens derived from the human body."

Essential Principles



Source: GHTF

Purpose

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

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

Purpose

"… 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 …

Purpose

"… These are grouped as: (continued)

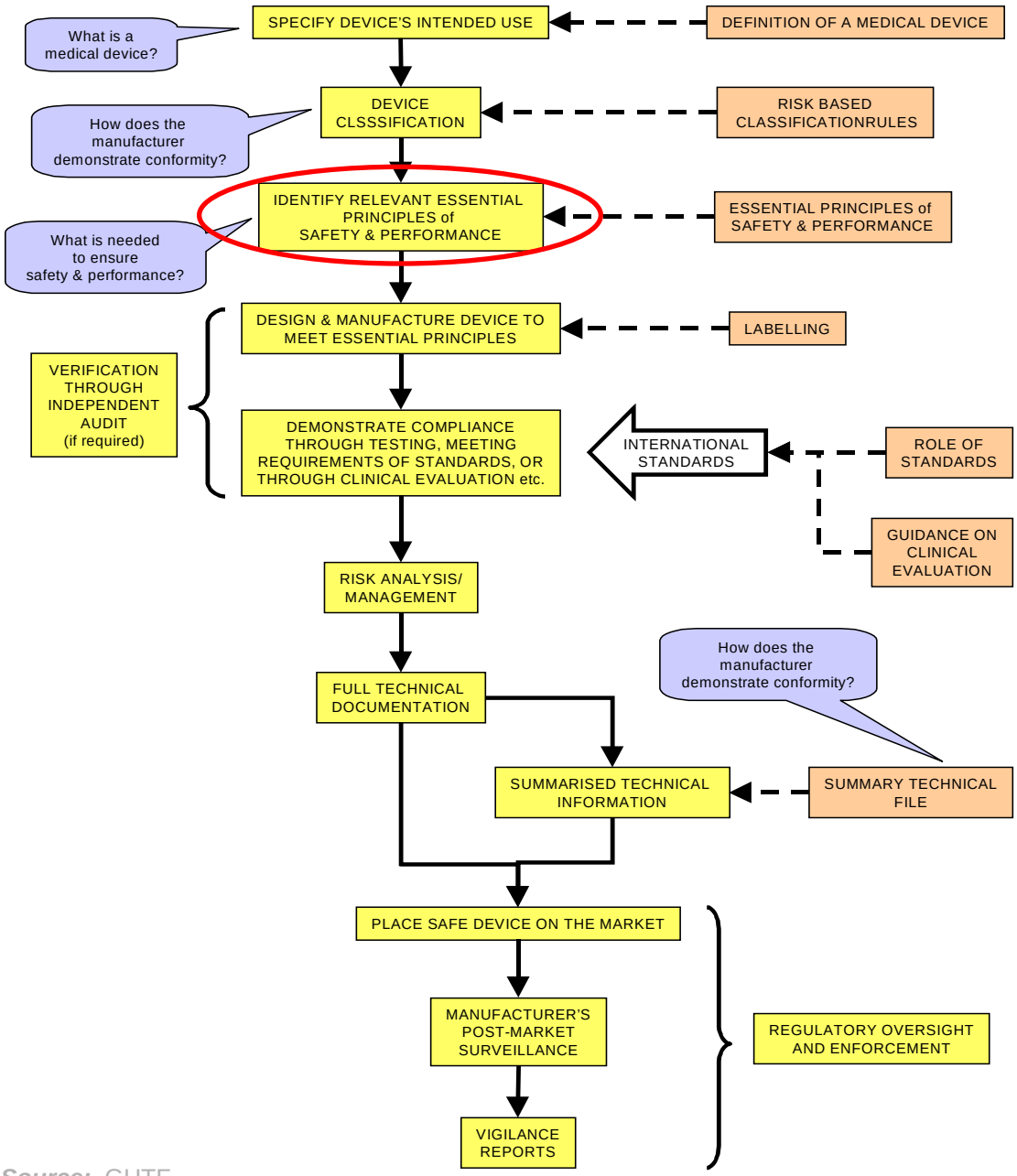
- Protection against the risks posed to the patient by supplied energy or substances
- Protection against the risks posed to the patient for devices for self-testing or self-administration
- Information supplied by the manufacturer
- Performance evaluation including, where appropriate, clinical evaluation"

Purpose

"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)

Essential Principles



Source: GHTF

General requirement 1

"Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training of intended users, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, …"

General requirement 1 (continued)

"… provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety."

General requirement 2

"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.

When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. …"

Reference: ISO 14971:2001: *Medical devices – Application of risk management to medical devices*

General requirement 2 (continued)

"The manufacturer should apply the following principles in the priority order listed:

- identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse,
- eliminate risks as far as reasonably practicable through inherently safe design and manufacture
- reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms,
- inform users of any residual risks"

General requirement 3

"Devices should achieve the performance intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions within the scope of the definition of a medical device applicable in each jurisdiction."

General requirement 4

"The characteristics and performances …. should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions."

General requirement 5

"The devices should be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected under transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer."

General requirement 6

"The benefits must be determined to outweigh any undesirable side effects for the performances intended"

Conformity assessment

"Refer to … *Principles of Conformity Assessment for Medical Devices* and the work of GHTF Study Group 5 for further information on the use of clinical evaluation to demonstrate compliance with these Essential Principles."

Summary

- Essential Principles form foundation of harmonised global regulatory model
- Comprehensive in scope
- Cover safety and performance
- Define design requirements
- Do not define methods of achieving, demonstrating, or documenting conformity
    - Often covered by international standards

Summary

- Manufacturer must apply all general principles and all relevant specific principles
- Flexible to accommodate advances in the state of the art and new medical devices / technologies / intended uses
- Recognise risks and benefits associated with medical devices
- Are founded on risk management principles
- Intimately linked to manufacturer's quality system for design, manufacture, and risk management

Questions?

Quality Management Systems: History and Evolution

4th APEC-Funded Seminar on Harmonization of Medical Device Regulation
Kuala Lumpur
March 5-7, 2008

Gunter Frey
Vice Chair SG3

Introduction

- What is a quality management system ?
- Why comply with a quality management system standard ?
- Evolution of quality practices

What is a quality management system for medical devices?

- ISO 13485:2003 Medical devices - Quality management systems - Requirements for regulatory purposes
- Regulatory variations (US FDA CFR 21 Part 820), Japanese MHLW Ordnance No. 169, 2004, etc.)
- “Full” quality management system includes design and development (mandatory for highest risk devices)
- “Production” quality management covers all activities except design and development

What is a quality management system for medical devices?

Quality Management System

"management system to direct and control an organization with regard to quality.

ISO 9000:2000, Clause 3.2.3.

Quality

"degree to which a set of inherent characteristics fulfils requirements"

ISO 9000:2000, Clause 3.1.1

Why should a manufacturer comply with a quality management system standard?

- Provides high degree of assurance that manufacturer will consistently produce medical devices that:
  - Are safe
  - Perform as intended
  - Comply with customer requirements
  - Comply with regulatory requirements
  - Have the appropriate degree of quality

Evolution of Quality – No Quality Efforts

1. **Design → manufacture → distribute →**

   Result: product may fail → customer complains

Evolution of Quality – Quality Control

2. **Design → manufacture → test → discard rejects → distribute accepted product → Results: Fewer failing product are distributed, but design problems may arise → Customer complains. Manufacturer is unhappy about rejects and waste**

Evolution of Quality – Quality Assurance & Good Manufacturing Practice (GMP)

3. **Design → build quality into manufacturing steps → control manufacture → test → discard rejects → distribute accepted product → Result: Fewer product rejects due to manufacturing. Manufacturer is happier, but design problems may still arise. Customer complains.**

Evolution of Quality – Quality System

4. **Build quality into design → build quality into manufacturing → control manufacture → Test → Discard rejects → Distribute accepted product → Results: Better-designed products satisfy customers. Manufacturer is happy with fewer rejects and fewer customer complaints**

Evolution of Quality – Quality Management Systems

Management has greater commitment to and responsibility for:

- establishing effective quality system,
- providing adequate resources
- periodically evaluating quality system
- making changes and adjustments

Summary

- What is a quality management system ?
- Why comply with a quality management system standard ?
- Evolution of quality practices

ISO13485:2003
- An Overview -

Gunter Frey / NEMA

Hideki Asai / JFMDA

Member, SG3

This presentation is based on

- **ISO13485:2003,** ***Medical devices - Quality management systems - Requirements for regulatory purposes***
- **ISO/TR 14969,** ***Medical devices - Quality management systems - Guidance on the application of ISO13485:2003***

This presentation focuses on the key sections of ISO13485:2003:

Section 4.0 - Quality Management System Requirements

Section 5.0 - Management Responsibility

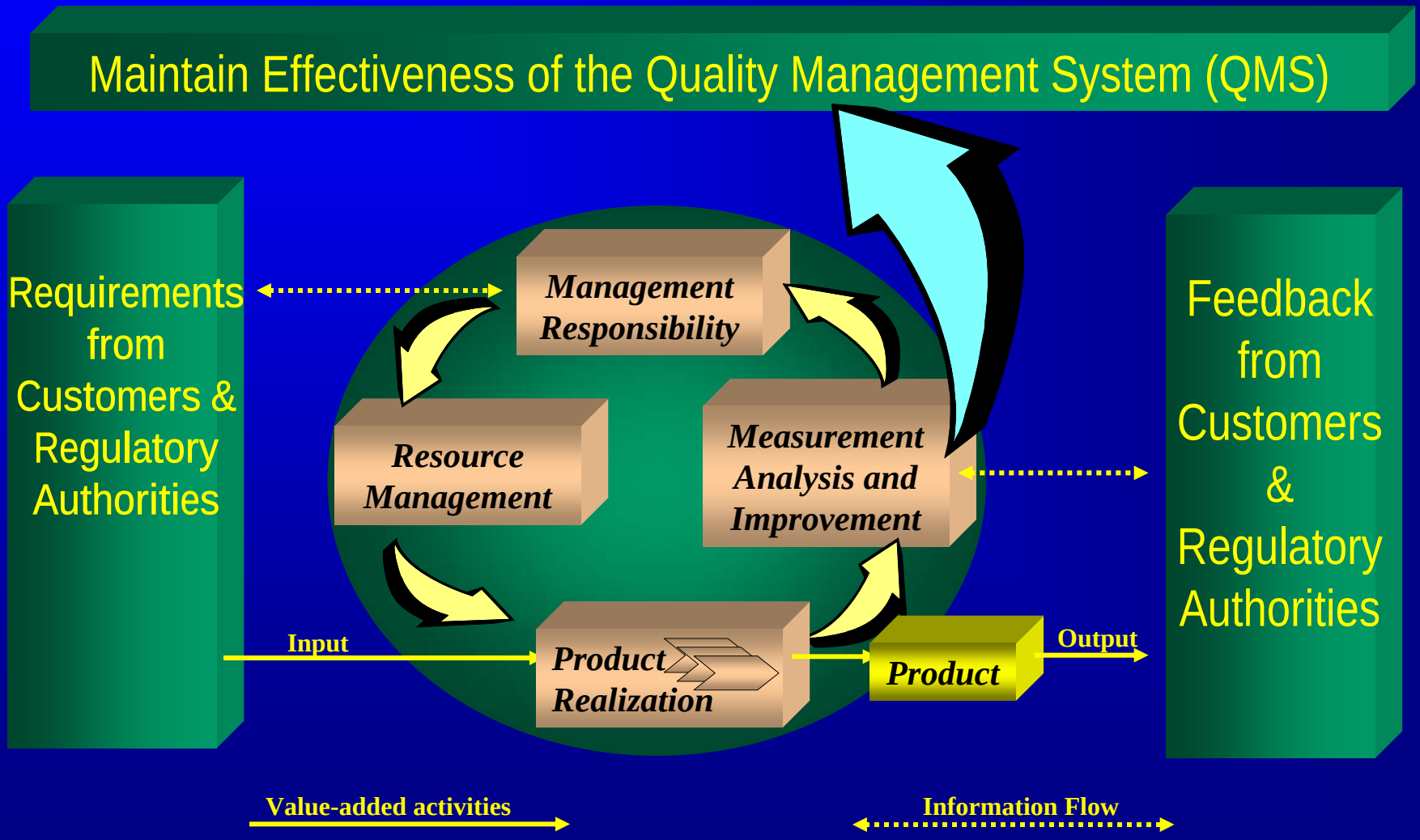
Section 6.0 - Resource Management

Section 7.0 - Product Realization

Section 8.0 - Measurement, Analysis, and Improvement

Process-oriented structure

ISO 13485:2003 promotes a process approach when developing, implementing, and improving a QMS



4. Quality Management System

4.1 - General requirements

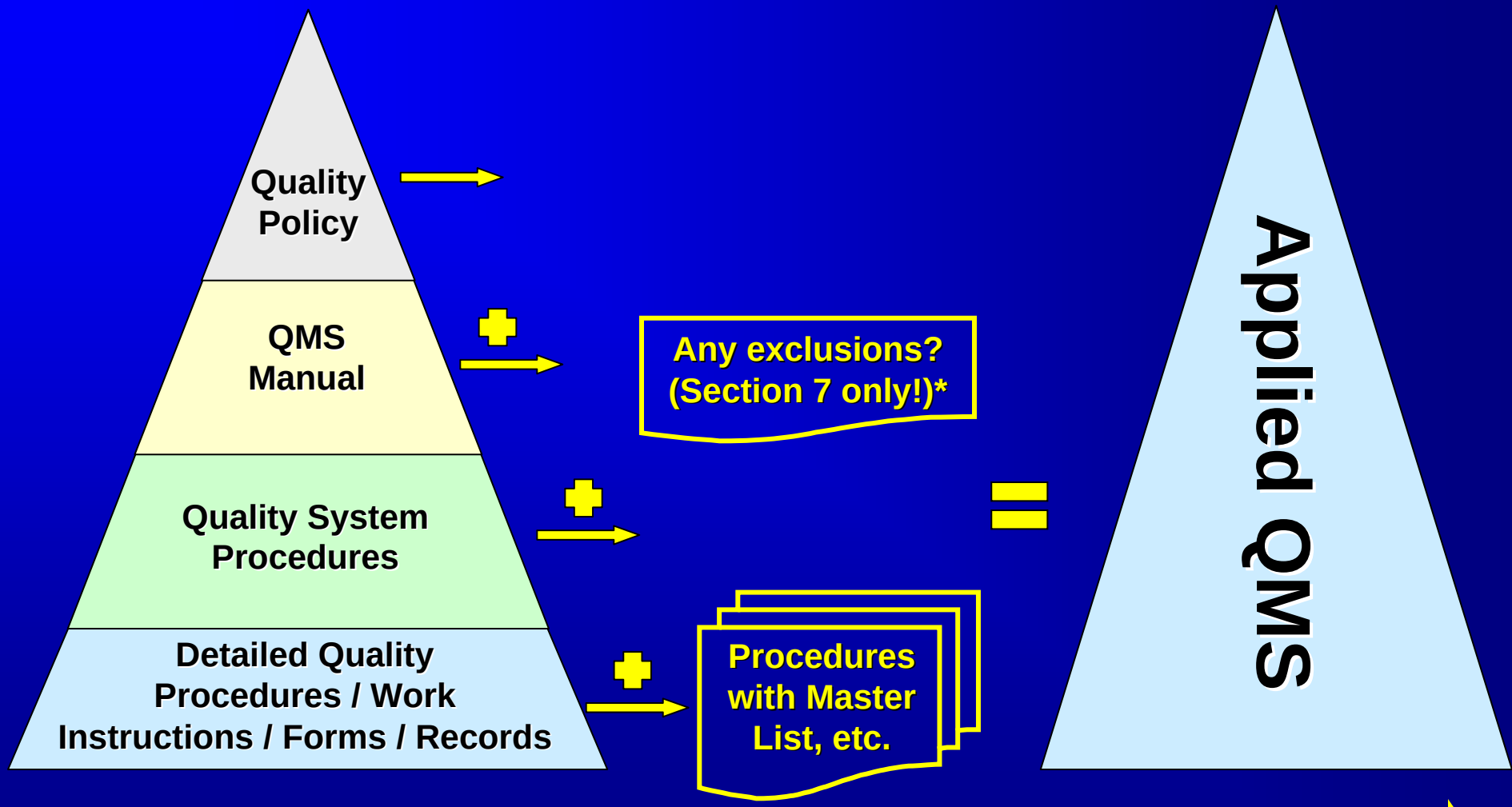
- Implementation and maintenance of an effective QMS to provide medical devices meeting customer and regulatory requirements.
- Ensure control of outsourced processes

Guidance Document SG3N17 currently being developed on what is considered adequate "control".

4.2 - Documentation requirements

- what is to be done and by whom, when, where, and how it is to be done, what materials, equipment and documents are to be used,
- how an activity is to be monitored and measured,
- Design History File, Technical File, Complaint File, device records, etc.

Quality System Definition



*see next slides

Product Realization - Exclusions

Exclusions of design and development (7.3) from the QMS is allowed only if allowed by regulation.
See NOTE 2 of 7.1: The organization ***MAY*** also apply the requirements given in 7.3 to the development of product realization processes.

Organizations whose quality management systems exclude design and development control (7.3 of ISO 13485), are still ***required to comply with the product verification and validation requirements as specified in 7.1 of ISO 13485 dealing with product realization*****.** In such organizations, the ***controls included in 7.3 should be considered for all changes made to the product***. Such changes will require objective evidence (e.g., product verifications and validations, inspection and test specifications, revised procedures, etc.) of the results of the activities described in 7.3 of ISO 13485.

Product Realization - Non-applicability

“Non-inclusion” of product realization requirements is allowed if those functions are not required by the nature of the medical device being provided by the organization.

For example, an organization providing single-use, sterile medical devices may not need to include within its quality management system elements related to installation and servicing.

5. Management Responsibility

5.1 Management commitment

- Is demonstrated by actions ensuring processes operate as an effective network of interrelated processes

5.2 Customer focus

- ensure customer requirements are understood

5.3 Quality policy

- Establishes commitment to: quality; continuing effectiveness of the quality management system; meeting customer and regulatory requirements
- Should be reviewed periodically for continued applicability

Case Study: Quality Policy

- The policy of Superior Devices, Inc., is to strive to sell products that satisfy our customers, comply with applicable standards and regulations, and reward employees who contribute substantially to our financial success with a share of our profits.
- Is this a good quality policy? Why or why not?

5. Management Responsibility

5.4 Planning

Includes:

- setting quality objectives & associated targets for the ***quality management system*** AND for ***medical devices & related services*** (see 7.1 a)
- defining timeframes for achieving targets

An organization's QMS is influenced by ***varying needs***, ***particular objectives***, the ***products provided***, the ***processes*** employed, the ***size & structure*** of the organization, etc.

5. Management Responsibility

5.4 Planning

Important

ISO13485 does **NOT** imply uniformity in the structure of quality management systems or uniformity of documentation!

5. Management Responsibility

5.5 Responsibility, authority and communication

Examples demonstrating Responsibility & Authority:

- documented position descriptions, including responsibilities and authorities
- organization charts
- can be included in documented procedures or flowcharts.
- Independence must be demonstrated for certain activities (e.g. internal audits, one design review participant; management representative)

Above documents must be controlled (see 4.2.3).

5. Management Responsibility

5.5 Responsibility, authority and communication

One management representative - designated by top management!

Functions can be entirely related to quality management system activities or in conjunction with other functions and responsibilities within the organization.

If responsibility for other functions, ensure no conflict of interest between the responsibilities!

5. Management Responsibility

5.5 Responsibility, authority and communication

Within an effective quality management system communications must be:

- encouraged
- clear and understandable
- bi-directional
- at all levels of the organization
- open and active

Examples: Internal audits, external assessments, management reviews, bulletin boards, all employee meetings, suggestion boxes, etc.

5. Management Responsibility

5.6 Management Review

Periodic assessment of the QMS for continued suitability, adequacy and effectiveness. **Inputs include:**

a) results of audits,
b) customer feedback,
c) process performance and product conformity,
d) status of preventive and corrective actions,
e) follow-up actions from previous management reviews,
f) changes that could affect the quality management system,
g) recommendations for improvement, and
h) new or revised regulatory requirements.

5. Management Responsibility

5.6 Management Review

Outputs include:

a) agenda
b) attendance record
c) presentation materials
d) improvements needed to maintain the effectiveness of the quality management system and its processes
b) improvement of product related to customer requirements
c) resource needs
d) statement of conclusion the effectiveness of the quality management system

Case Study: Management Reviews Part 1

- Perfect Devices, Inc., (PD) established their quality system 5 years ago, and things have been running smoothly. They have been producing the same devices for the past 5 years. The FDA inspection 6 months ago was NAI. PD performs management reviews annually.
- Is an annual management review sufficient?

Case Study: Management Reviews Part 2

- Superior Medical, Inc., (SM) established their quality system 5 years ago. This year's production was double that of 5 years ago. Six months ago SM installed an ethylene oxide sterilization chamber and started distributing sterile devices. Several sterilization lots have failed. SM performs management reviews annually.
- Is an annual management review sufficient?

6. Resource Management

6.1 Provision of resources

Resources can be:

- people
- infrastructure
- work environment
- information
- suppliers and partners
- natural resources
- financial resources

Adequate resources are prerequisite to an effective QMS

6. Resource Management

6.2 Human Resources

Personnel performing work affecting product quality and device safety and effectiveness must be competent ….

- Qualifications include:
  - Education
  - Experience
  - Skills
  - EFFECTIVE Training (initial and refresher)
  - Formal certification (e.g. welding, soldering)

- Organization must be able to demonstrate this!

6. Resource Management

6.3 Infrastructure

Includes:

- Buildings
- Work space
- Utilities (water, electricity, waste management, etc.)
- Process equipment (software and hardware)
- Equipment maintenance activities & frequency
- Supporting services (cleaning, etc.)

If not considered and appropriately defined, the above examples can potentially affect conformance with product requirements!

Case Study: Facilities

- Oops! An existing piece of equipment was moved to make room for some new equipment. When scheduled maintenance was due on the first piece of equipment, the maintenance man was unable to perform these tasks, as the equipment was too close to the wall. He got creative and suggested installing doors in the wall to allow access to that side of the equipment. This is an outside wall!
- Is this an acceptable solution? Why or why not?

6. Resource Management

6.4 Work Environment

The most significant factors within the work environment that can affect product quality are:

- process equipment,
- established work environment (controlled environments, clean rooms, etc.)
- personnel – internal and ***external***! (health, cleanliness, protective equipment/gear, i.e. static dissipating wrist bands, hoods & gowning, etc.)

"Established" means defined, documented, implemented and maintained!

Case Study: Clean Rooms

- An electrical outlet in the clean room is not working, and an electrician has been called to replace it. SOPs (procedures) require employees who work in the clean room to wear a hair cover, face mask, shoe covers, lab coat and gloves.
- Should the electrician follow the same gowning procedures? Why or why not?

7. Product Realization

7.1 Planning of product realization

"Product realization" describes the processes starting with

- planning
- determination of customer requirements
- customer communication
- design and development (7.3),
- purchasing (7.4),
- production and servicing (7.5),
- control of monitoring and measuring devices (7.6)
- delivery of the medical device
- record keeping requirements

7. Product Realization

7.1 Planning of product realization

The organization shall determine :

- product quality objectives & requirements
- definition of medical device lifetime (record retention!)
- establishing processes & documents
- resource needs
- design and development (7.3),
- verification & validation
- monitoring and inspection
- test activities and product acceptance criteria
- **RISK MANAGEMENT**
- RECORDS

SG3/N15R8/2005 " Implementation of Risk Management Principles and Activities Within a Quality Management System" published in 2005

GHTF SG3 N15 Integrate Risk Management throughout product realization

- ISO 13485 requires the organization to establish documented requirements for risk management throughout product realization and suggests that ISO 14971 be consulted for guidance.

- SG3 developed SG3/N15R8/2005 to provide guidance on how to integrate risk management activities (for example those described in ISO 14971) into an ISO 13485:2003 based QMS.

7. Product Realization

7.2 Customer-related processes

Focus is on product and services to be supplied. This includes requirements related to the product:

- design input/output for new product development,
- customer delivery expectations vs. delivery schedules
- customer feedback & communications relative to orders placed or product delivered
- regulatory or legal requirements
- design related factors included in customer orders
- unspecified customer expectations.

7. Product Realization

7.2 Customer-related processes

Review of product requirements prior to committing to supply:

- product requirements defined & documented
- resolution of contract/order discrepancies
- ensure ability to meet defined requirements

Review of post-marketing product performance

- additional product information (e.g. service, additional applications, maintenance, upgrades)
- customer complaints
- advisory notices

Again, records are key!

7. Product Realization

7.3 Design and development

Established procedures describing design processes and ALL design activities

- goals and objectives of the design and development program (i.e. what is to be developed, timeline, etc.)
- the markets intended
- identification of organizational responsibilities with respect to assuring quality during the design and development phase, to include interface with any suppliers
- identification of the major tasks by phases of the design
- expected outputs (deliverables and records) from each phase

7. Product Realization

7.3 Design and development

Established procedures describing design processes and ALL design activities (cont.)

- identification of appropriate existing and anticipated measurement & monitoring devices for development of product specifications, verification, validation and production related activities
- the selection of reviewers & composition of review teams
- planning transfer to production
- risk management activities
- supplier selection

7. Product Realization

7.3 Design and development

Design inputs include:

- intended use of the device,
- Indications and contra-indications for use of the device,
- performance claims and performance requirements (including normal use, storage, handling and maintenance),
- user and patient requirements,
- physical characteristics,
- human factors/usability requirements,
- safety and reliability requirements,
- toxicity and biocompatibility requirements,

7. Product Realization

7.3 Design and development

Design inputs (cont.):

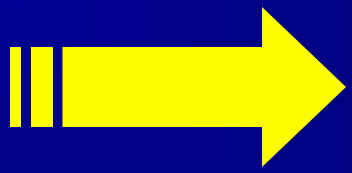
- electromagnetic compatibility requirements,
- limits/tolerances,
- measurement and monitoring instruments,
- risk management or risk reduction methods
- reportable adverse events, complaints, failures for previous products,
- other historical data,
- documentation for previous designs,
- compatibility requirements with respect to accessories and auxiliary devices,

7. Product Realization

7.3 Design and development

Design inputs (cont.):

- compatibility requirements with respect to the environment of intended use,
- packaging and labeling (including considerations to deter foreseeable misuse),
- customer/user training requirements,
- regulatory and statutory requirements of intended markets,
- relevant voluntary standards (including industry standards, national, regional or international standards, “harmonized” and other consensus standards),



7. Product Realization

7.3 Design and development

Design inputs (cont.):

- manufacturing processes,
- sterility requirements,
- economic and cost aspects,
- lifetime of the medical device requirements, and
- need for servicing.

Case Study: Hospital vs. Home Use

- For several years Advanced Devices has been selling a patient monitor for use in the hospitals. Recently one of their salespeople suggested marketing the patient monitor for home use since patients are spending less and less time in the hospital.
- Will home use change the design input? Why or why not?

Case Study: Hospital vs. Home Use

Considerations:

- User less skilled, no medical training
- Users impaired? Poor vision, poor manual dexterity?
- User environment different; electromagnetic interference from TV, cell phones, etc.
- Multiple users, etc.

7. Product Realization

7.3 Design and development

Design outputs may include:

- specifications for raw materials, component parts and sub-assemblies,
- drawings and parts list,
- customer training materials,
- process and materials specifications,
- finished medical devices,
- product and process software,
- quality assurance procedures (including acceptance criteria),
- manufacturing and inspection procedures,

7. Product Realization

7.3 Design and development

Design outputs (cont):

- work environment requirements needed for the device,
- packaging and labeling specifications,
- identification and traceability requirements (including procedures, if necessary),
- installation and servicing procedures and materials,
- documentation for submission to the regulatory authorities where the medical devices will be marketed, if appropriate, and
- a record/file to demonstrate that each design was developed and verified in accordance with the design and development planning

7. Product Realization

7.3 Design and development

Design reviews may address the following questions:

- Do designs satisfy specified requirements for the product?
- Is the input adequate to perform the design and development tasks?
- Are product design and processing capabilities compatible?
- Have safety considerations been addressed?
- What is the potential impact of the product on the environment?
- Do designs meet functional and operational requirements, for example, performance and dependability objectives?

7. Product Realization

7.3 Design and development

Design reviews (cont.):

- Have appropriate materials been selected?
- Have appropriate facilities been selected?
- Is there adequate compatibility of materials, components and/or service elements?
- Is the design satisfactory for all anticipated environmental and load conditions?
- Are components or service elements standardized and do they provide for reliability, availability and maintainability?
- Is there a provision in tolerances, and/or configuration, for interchangeability and replacement?

7. Product Realization

7.3 Design and development

Design reviews (cont.):

- Are plans for implementing the design technically feasible (e.g. purchasing, production, installation, inspection and testing)?
- If computer software has been used in design computations, modeling or analyses, has the software been validated, authorized, verified and placed under configuration control?
- Have the inputs to such software, and the outputs, been appropriately verified and documented?
- Are the assumptions made during the design processes valid?

Case Study: Design Review

- Can a formal design review be conducted without holding a meeting?
- Would circulating design review issues and approving outcomes by e-mail or on paper be an acceptable alternative to holding a meeting?

Case Study: Design Review

- Nowhere in the standard or the guidance is it stated that a design review must be conducted by holding a meeting!
- If all design review requirements of the standard are met, the design review could take place by e-mail or review of paper summary.
- Design reviews conducted by e-mail or paper probably are best used for relatively simple reviews.

Case Study: Design Review

- Please keep in mind that additional requirements may exist for electronic records, as well as electronic signatures.

- If design reviews are conducted via e-mail or paper copy circulation, results of the review will still need to be documented. Documentation typically includes identifying attendees, which is best done by signatures next to printed name. Print a signature page from the e-mail, sign and scan it and retain in the Design History File.

Case Study: Design Review

- Persons making authorized entries on records or verifying such entries should do so in clear legible writing, and should confirm the entry by adding their initials, signature or equivalent, and the date (14969 guidance).

7. Product Realization

7.3 Design and development

Design verification is necessary to ensure that the design outputs conform to specified requirements (design inputs).

- tests (bench tests, lab tests, chemical analysis, etc.)
- alternative calculations,
- comparison with proven design,
- inspections, and
- document reviews (e.g. specifications, drawings, plans, reports).

7. Product Realization

7.3 - Design and development

Design validation goes beyond the technical issues of verifying output met input. It is intended to ensure that the medical device meets user requirements and the intended use.

- actual or simulated conditions
- consider capability and knowledge of user
- operating instructions
- compatibility with other systems
- the environment in which it will be used
- any restriction on the use of the product
- performed on production or production equivalent unit(s)

If production equivalent – need to document why it is equivalent!

7. Product Realization

7.3 Design and development
Control of design and development changes

- Product design may require change or modification for many reasons.
- Change can happen during or after the design phase
- Changes may result from:
  - design review
  - design verification or validation
  - omissions or errors during the design phase which have been identified afterwards

7. Product Realization

7.3 Design and development

- Changes may result from:
  - difficulties in manufacturing, installation and/or servicing
  - risk management activities,
  - requests from the customer or supplier,
  - changes required for corrective or preventive action
  - changes needed to address safety, regulatory, or other requirements
  - improvements to function or performance

7. Product Realization

7.3 Design and development

- When changes are necessary, evaluate effects on:
  - product requirements and specifications
  - intended use
  - current risk assessment
  - different components of the product or system
  - manufacture, installation or use
  - Verification and validation
  - the regulatory status of the product

7. Product Realization

7.4 Purchasing

Guidance Document SG3N17
currently being developed on what is adequate "control".

Supplier selection and control consists of:

- establishing criteria (product, parts, quality system, process controls, metrology, etc.)
- evaluating against those predetermined criteria
- selecting
- ongoing monitoring

The extent depends on the nature and risk associated with the product or service, and includes outsourced processes.

Purchasing should only occur from list of approved suppliers!

Case Study: Purchasing Controls

- Perfect Devices, Inc. is evaluating potential suppliers of a plastic resin for injection molded parts. Perfect contacted several potential suppliers to schedule audits to evaluate them, but two large firms have declined to be audited.
- What should Perfect Devices, Inc. do?

1. Buy only from firms allowing audits?
2. Find another way to evaluate large firms?
3. Other alternatives?

7. Product Realization

7.4 Purchasing

Purchasing information describes the product to be purchased in sufficient detail, such as:

- technical information and specifications,
- test and acceptance requirements,
- quality requirements for products, services, and outsourced processes,
- environmental requirements (in manufacturing, storage, transportation, etc.)
- regulatory requirements,
- certification requirements

Case Study: Incoming Acceptance - 1

- Perfect Devices, Inc. recently selected three new suppliers based on the following information:
  1. Aim To Please, Inc.: Supplier audit documented an excellent quality system.
  2. A-1 Plastics: Refused audit, highly recommended by other device manufacturers.
  3. OK Parts, Inc.: Sole source of component! Supplier audit: No quality system!
- Which approach to acceptance of incoming components would you recommend for each supplier?

Case Study: Incoming Acceptance - 2

Aim to Please, Inc. - A-1 Plastics - OK Parts, Inc.

From ANSI.ASQ Z1.4:

1. “Tightened Inspection followed by normal inspection when 5 consecutive lots are acceptable
2. “Normal Inspection” followed by reduced inspection and 10 consecutive lots are accepted and additional criteria in 8.3.3.b are met.

7. Product Realization

7.4 Purchasing

Purchasing information (cont.):

May also include:

- requirements for product approval and subsequent changes
- procedures, processes & equipment
- qualification of personnel
- QMS requirements
- method of communication
- responsibilities (special instructions, traceability & test records, record retention & retrievability, etc.)
- conditions for review & changes to purchasing agreement

SUPPLIER RECORDS and the **ORGANIZATION'S RECORDS**

7. Product Realization

7.4 Purchasing

Verification of purchased product to ensure specified requirements are met:

- receiving Inspection (shipments are complete, properly identified, undamaged)
- product incoming inspection (100%, sampling, skip lot, etc.)
- certification of suppliers
- certificates of conformance or acceptance test reports from supplier

Must be procedurally defined within the organization's QMS, ***including actions when requirements are not met***!

Applies to *ALL product received from outside the organization's QMS*!

7. Product Realization

7.5 Production and service provision

Control of production and service requires ***controlled conditions*** and includes many aspects:

- infrastructure (see 6.3)
- documentation and records (procedures, specifications, work instructions, test results, etc.)
- defined by *impact on quality* & *regulatory requirements* as well as *output from risk management activities*
- suitable equipment (process, measurement, monitoring)
- activities for release, delivery, and post delivery, including traceability

Records are key!

Case Study: Installation Instructions

- Zap Em, Inc. manufactures linear accelerators for radiation therapy for cancer. Zap Em installs the equipment for a significant fee. Hospitals have requested installation instructions for self-installation. Zap Em says they would be glad to provide instructions and equipment if the hospital employees attend Zap Em's 2 day installer training for $9,500.
- Is Zap Em entitled to withholding instructions from 3rd party installers unless they attend a training course?

7. Product Realization

7.5 Production and service provision

Validation of processes for production & service is required where the resulting output cannot be verified!

Guidance document
SG3/N99-10 (Edition 2) " Quality Management Systems - Process Validation Guidance." published.

- defined criteria for review and approval of processes
- approval of equipment and ***personnel qualification*** 
- use of specific methods and procedures
- criteria for revalidation 
- software used in automated processes **MUST** be validated 

7. Product Realization

7.5 Production and service provision
Validation of processes for production & service (cont.)

Process validation activities can be described in phases:

- definition, review and approval of equipment specifications
- installation qualification (IQ)
- operational qualification (OQ)
- performance qualification (PQ)

Validation is a complex activity – SG 3 has developed specific guidance on this topic (GHTF/SG3/N99-10:2004).
A separate presentation “Process Validation Guidance” addresses this in greater detail.

7. Product Realization

7.5 Production and service provision

Identification is required throughout the product realization process. It includes:

- raw materials
- components
- finished medical devices

This facilitates fault diagnosis in the event of quality problems and is a pre-requisites for traceability!

Provisions for identifying & segregating returned medical devices from conforming product must also be established!

7. Product Realization

7.5 Production and service provision

Traceability means the ability to trace the history or location of a product or activity by recorded identification:

- forward to customers (also known as “device tracking”)
- backward to raw materials, components, processes used in manufacturing, calibration, etc.

Example: trace a nonconformity back to it’s source and determine location of the remainder of the affected batch/series.

Particular requirements are defined for implantable devices!

7. Product Realization

7.5 Production and service provision

Customer property within the context of the standard is defined as property or assets owned by the customer and under control of the organization.

Examples of such property are

- raw materials or components supplied for inclusion in product (including packaging materials),
- product supplied for repair, maintenance or upgrading,
- product supplied for further processing (e.g., packaging, sterilization or testing),
- customer intellectual property

These must be properly identified, safeguarded, maintained, etc.

7. Product Realization

7.5 Production and service provision

Preservation of product applies throughout the product realization processes and includes storage, handling, transportation and delivery (may include installation).

- gloves, static-dissipative measure, gowning,
- temperature, humidity, dust (particle count),
- packaging
- method of transportation (air, sea, ground, environmentally controlled, etc.)

To avoid damage, deterioration or contamination during handling, storage, distribution.

7. Product Realization

7.6 Control of monitoring and measuring devices

The standard explicitly refers to monitoring and measuring devices, **including software**. To ensure valid results, instruments shall be

- calibrated or verified at specified intervals (traceable to standard!)
- uniquely identified (traceability to products!)
- protected from damage/deterioration or inadvertent adjustment during storage and use

Software used in the monitoring or measurement process must be validated!

Exempt from calibration may be: instruments used for indication only (not quantitative!), volumetric measurement glassware, etc.

8. Measurement, analysis and improvement

8.1 General

Monitoring and measurement processes are required to:

- ensure product conformance
- ensure conformance of the QMS
- maintain effectiveness of the QMS

These processes include measurement and analysis of products AND processes.

8. Measurement, analysis and improvement

8.2 Monitoring and Measurement

Feedback as key performance indicators of the QMS include:

- customer related information, post-market surveillance, etc.)
- internal & external audit results
- monitoring and measurement of processes (not limited to production processes but also QMS processes!)
- monitoring and measurement of product (may extend to point of installation!)

8. Measurement, analysis and improvement

8.3 Control of nonconforming product

This includes nonconforming product occurring in the organization's own facilities as well as to nonconforming product **received** or **delivered** by the organization.

- determine product(s) affected
- identify the nonconforming product (at supplier, in house, in transit, at customer)
- document the existence and root cause of the nonconformity
- evaluate the nature of the nonconformity

8. Measurement, analysis and improvement

8.3 Control of nonconforming product (cont.)

- determine and record disposition to be made,
- control (e.g. by physical segregation) the subsequent processing of the nonconforming product consistent with the disposition decision
- notify others as appropriate (regulatory authorities, customer, supplier, alternate manufacturing facilities, etc.)
- define and implement **corrective** and **preventive** actions
- assess the effectiveness of corrective and preventive actions

8. Measurement, analysis and improvement

8.4 Analysis of data

This includes determination, collection, and analysis of appropriate data to demonstrate the

- suitability and effectiveness of the QMS and
- to evaluate if improvement of the QMS effectiveness can be made.

This encompasses supplier performance, product conformance, trends of processes & products, feedback, etc.

The results of these activities should feed into management reviews as well considered for risk management activities. They also serve to identify opportunities for preventive actions.

Case Study: Data Analysis

- Which items below would be appropriate data sources to analyze to identify non-conforming product and quality problems?

1. Incoming Acceptance Records
2. Complaints
3. Service Records
4. Sales Figures
5. Internal Audits
6. Records of Installation
7. Customer Lists
8. Reports of external audits
9. Personnel Records
10. Lawsuits
11. Finished device Acceptance Records
12. In process Acceptance Records

Case Study: Data Analysis

- Which items below would be appropriate data sources to analyze to identify non-conforming product and quality problems?

1. **Incoming Acceptance Records**
2. **Complaints**
3. **Service Records**
4. Sales Figures
5. **Internal Audits**
6. **Records of Installation**
7. Customer Lists
8. **Reports of external audits**
9. Personnel Records
10. **Lawsuits**
11. **Finished device Acceptance Records**
12. **In process Acceptance Records**

8. Measurement, analysis and improvement

8.5 Improvement

This again covers a broad scope:

- continued suitability and effectiveness of the QMS
- documented complaint investigations and resulting actions
- product advisory notices (field corrective actions, etc.) communicated to customers and (where applicable) to regulatory authorities

8. Measurement, analysis and improvement

8.5 Improvement

Corrective action is intended to eliminate nonconformities with the intent to prevent recurrence. Nonconformities may be identified

- in the QMS
- on the product
- in manufacturing processes
- in metrology
- with training
- environmental conditions
- control of equipment
- with suppliers, etc.

SG3 has identified the need to develop guidance documents on "significance of nonconformities" and "CAPA principles and practices"

8. Measurement, analysis and improvement

8.5 Improvement

Effective **corrective action** includes the following:

- clear and accurate identification of the nonconformity
- affected process(es) or procedure(s)
- identification of affected device(s) and recipient(s)
- identification of the root cause of the nonconformity,
- action required to prevent recurrence
- required approvals prior to taking action
- records that corrective action was taken as identified
- Effectiveness checks (likely to prevent recurrence, no new risks introduced by the corrective action, etc.)

8. Measurement, analysis and improvement

8.5 Improvement

Preventive action is initiated to address ***potential*** nonconformities. Sources to consider include information & data from:

- receiving and incoming inspection
- products requiring rework, reject or yield data
- customer feedback and warranty claims,
- process measurements,
- identification of results that are out-of-trend but not out-of-specification,
- suppliers performance
- service reports, and,
- concessions/deviations.

While the information covered during this session is based on ISO13485:2003 and ISO/TR14969,

it essentially describes

GOOD BUSINESS PRACTICES.

If successfully implemented, the organization's quality system will meet the requirements of the European Medical Device Directive (MDD 93/42/EEC).

LNE
G MED
Certification Médical-Santé

CERTIFICAT
CERTIFICATE OF REGISTRATION
N° 1030 / 13485 / 1

Le LNE certifie que le système qualité développé par
LNE certifies that the quality assurance system developed by

GE Medical Systems, LLC
3000 North Grandview Blvd.
WAUKESHA, WI 53188
USA

pour les activités / *for the activities*

Conception, fabrication, contrôle final de dispositifs ou systèmes de diagnostic tomodensitomètre par émission de positron, dispositifs ou systèmes de diagnostic X-Ray, dispositifs ou systèmes de diagnostic tomodensitomètres (scanners), gaines équipées (gaine + tube radiogène)
Design, manufacture, final test of medical diagnostic positron emission tomography devices or systems, medical diagnostic X-Ray devices or systems, diagnostic computed tomography devices or systems, X-ray tube assembly (housing + tube)

réalisées sur le site de / *performed on the location of*

GE Medical Systems, LLC
3000 North Grandview Blvd.
WAUKESHA, WI 53188, *USA*

GE Medical Systems, LLC
4855 Electric Avenue
MILWAUKEE 53219 - USA

est conforme aux exigences de la norme internationale
complies with the requirements of the international standard

ISO 13485 (2003)

Date de délivrance : 31 mars 2005
Date of issue : March 31, 2005

Date d'échéance de validité : 20 décembre 2005 (inclus)
Limit expiry date : December 20, 2005 (included)

Pour Le Directeur Général
For the general Director
Laurence DAGALLIER
Directeur Certification
Certification Director

cofrac

2004-12-15

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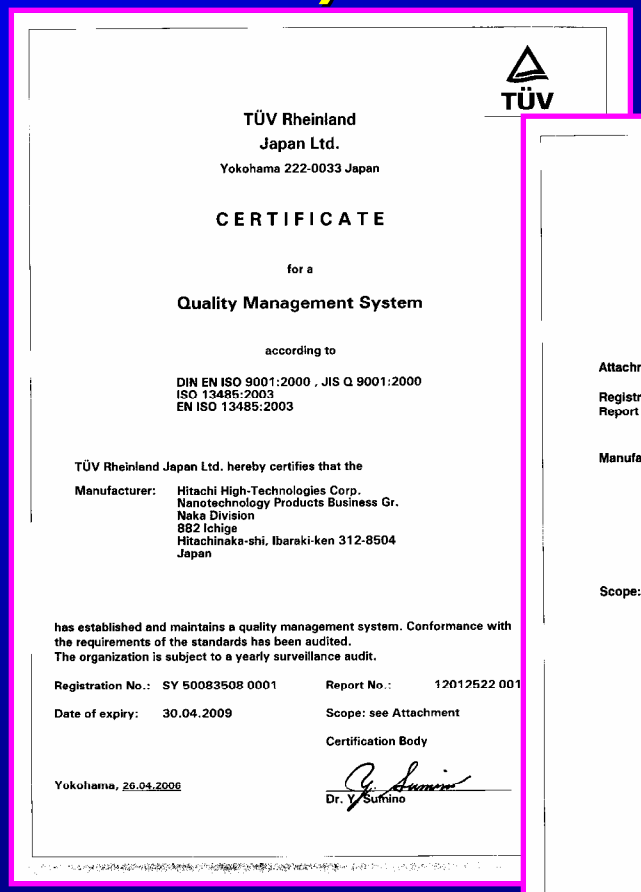


TÜV

TÜV Rheinland
Japan Ltd.
Yokohama 222-0033 Japan

CERTIFICATE

for a

Quality Management System

according to

DIN EN ISO 9001:2000 , JIS Q 9001:2000
ISO 13485:2003
EN ISO 13485:2003

TÜV Rheinland Japan Ltd. hereby certifies that the

Manufacturer: Hitachi High-Technologies Corp.
Nanotechnology Products Business Gr.
Naka Division
882 Ichige
Hitachinaka-shi, Ibaraki-ken 312-8504
Japan

has established and maintains a quality management system. Conformance with the requirements of the standards has been audited.
The organization is subject to a yearly surveillance audit.

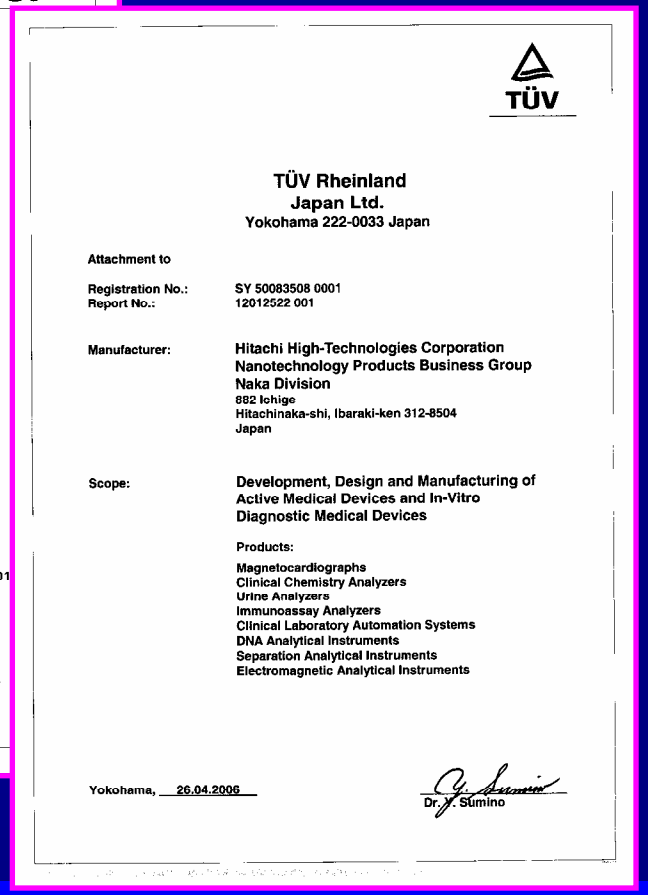
Registration No.: SY 50083508 0001 Report No.: 12012522 001

Date of expiry: 30.04.2009 Scope: see Attachment

Certification Body

Yokohama, 26.04.2006

Dr. Y. Sumino



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TÜV Rheinland
Japan Ltd.
Yokohama 222-0033 Japan

Attachment to

Registration No.: SY 50083508 0001
Report No.: 12012522 001

Manufacturer: Hitachi High-Technologies Corporation
Nanotechnology Products Business Group
Naka Division
882 Ichige
Hitachinaka-shi, Ibaraki-ken 312-8504
Japan

Scope: Development, Design and Manufacturing of Active Medical Devices and In-Vitro Diagnostic Medical Devices

Products:

Magnetocardiographs
Clinical Chemistry Analyzers
Urine Analyzers
Immunoassay Analyzers
Clinical Laboratory Automation Systems
DNA Analytical Instruments
Separation Analytical Instruments
Electromagnetic Analytical Instruments

Yokohama, 26.04.2006

Dr. Y. Sumino

For further guidance, please refer to

ISO/TR 14969

Thank you on behalf of Study Group 3 and the GHTF for your time and attention.

Questions?

APPENDIX

Examples of Key Records

- Management Review (5.6.1)
- Education, training, skills and experience (6.2.2.e)
- Product realization processes (7.1.d)
- Product requirements review and action (7.2.2)
- Product requirements inputs (7.3.2)
- Design reviews and actions (7.3.4)
- Design verification and actions (7.3.5)
- Design validation and actions (7.3.6)
- Design changes (7.3.7)
- Design change reviews (7.3.7)

Examples of Key Records (cont.)

- Supplier evaluation and actions (7.4.1)
- Process validation (7.5.2)
- Traceability (7.5.3)
- Customer notification regarding damage to customer property (7.5.4)
- Production or service delivery, as determined to be necessary for special processes (7.5.2)
- Review of previous measuring results when measuring equipment is found not to conform to requirements (7.6)
- Calibration or verification (7.6)

Examples of Key Records (cont.)

- Internal audits (8.2.2)
- Product release authorization (8.2.4)
- Nonconformities and actions taken (8.3)
- Corrective actions taken (8.5.2 e)
- Preventive actions taken (8.5.3 d)

GHTF.SG3.N15-R8
Implementation of Risk Management Principles and Activities Within a Quality Management System

Gunter Frey / NEMA

Hideki Asai / JFMDA

Member, SG3

- **Medical device manufacturers are generally required to have a quality management system as well as processes for addressing device related risks.**
- **These processes have become stand alone management systems.**

- **While manufacturers may choose to maintain these two management systems separately, it may be advantageous to integrate them as it could reduce costs, eliminate redundancies, and lead to a more effective management system.**

- **This document is intended to assist medical device manufacturers with the integration of a risk management system or the risk management principles and activities into their existing quality management system by providing practical explanations and examples**

- **The document is based on general principles of a quality management system and general principles of a risk management system and not on any particular standard or regulatory requirement.**

- An effective quality management system is essential for ensuring the safety and performance of medical devices.
- It includes safety considerations in specific areas.
- Given the importance of safety, it is useful to identify some key activities that specifically address safety issues and ensure appropriate input and feedback from these activities into the quality management system.

- **The degree to which safety considerations are addressed should be commensurate with the degree of the risk, the nature of the device and the benefit to the patient.**
- **Some devices present relatively low risk or have well-understood risks with established methods of risk control.**

In general, risk management is characterized by four phases of activities:

1. **Determination of acceptable levels of risk**
2. **Risk analysis**
3. **Determination of risk reduction measures**
4. **Risk control and monitoring activities**

Determination of acceptable levels of risk:

- Risk acceptability criteria should be defined.
- These criteria may come from:
  - an analysis of the manufacturer's experience with similar medical devices
  - currently accepted risk levels by regulators, users, or patients, given the benefits from diagnosis or treatment with the device.
- The criteria should be reflective of state-of-the-art in controlling risks.

Risk analysis:

- This phase starts with identifying hazards that may occur due to characteristics or properties of the device during normal use or foreseeable misuse.
- After hazards are identified, risks are estimated for each of the identified hazards, using available information.

Determination of risk reduction measures:

- In this phase, the estimated risks are compared to the risk acceptability criteria.
- This comparison will determine an appropriate level of risk reduction. This is called risk evaluation.
- The combination of risk analysis and risk evaluation is called risk assessment.

Risk control and monitoring activities:

- Actions intended to eliminate or reduce each risk to meet the previously determined risk acceptability criteria.
- One or more risk control measures may be incorporated.
- Risk controls may begin as early as design input and continue over the medical device life time.

Risk control and monitoring activities:

- Some regulatory schemes prescribe a fixed hierarchy of risk controls that should be examined in the following order:
  - Inherent safety by design
  - Protective measures in the device or its manufacture
  - Information for safety, such as warnings, maintenance schedules, etc.

Risk control and monitoring activities:

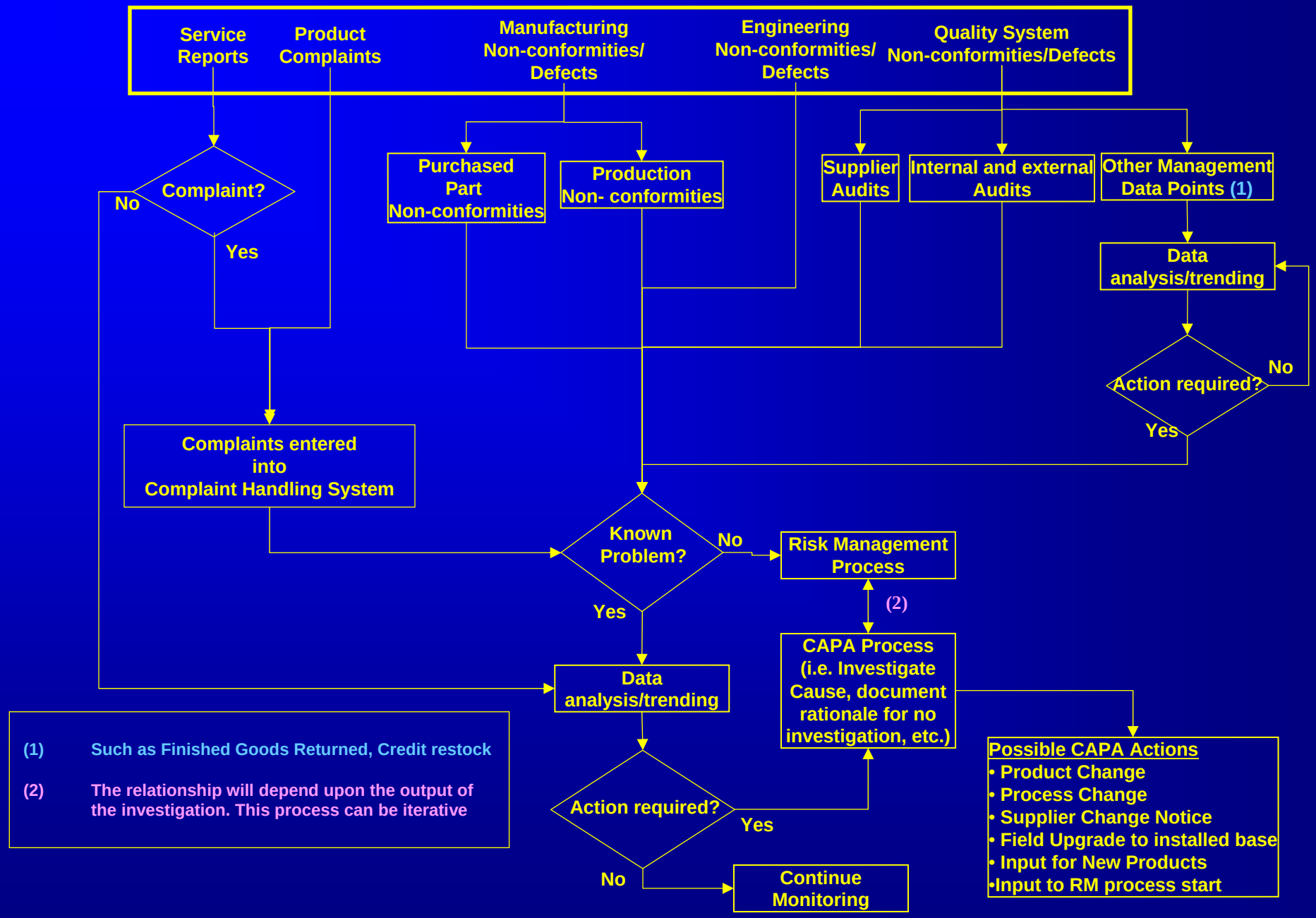
- Throughout the life-cycle of the device the manufacturer monitors whether the risks continue to remain acceptable and whether any new hazards or risks are discovered.
- An effective and well defined Quality Management System is key!

Risk control and monitoring activities:

- Information typically obtained from the quality management system, for example, production, complaints, customer feedback, should be used as part of this monitoring.

Let's examine this a little closer …

Key Quality Data Points



(1) Such as Finished Goods Returned, Credit restock

(2) The relationship will depend upon the output of the investigation. This process can be iterative

Risk control and monitoring activities:

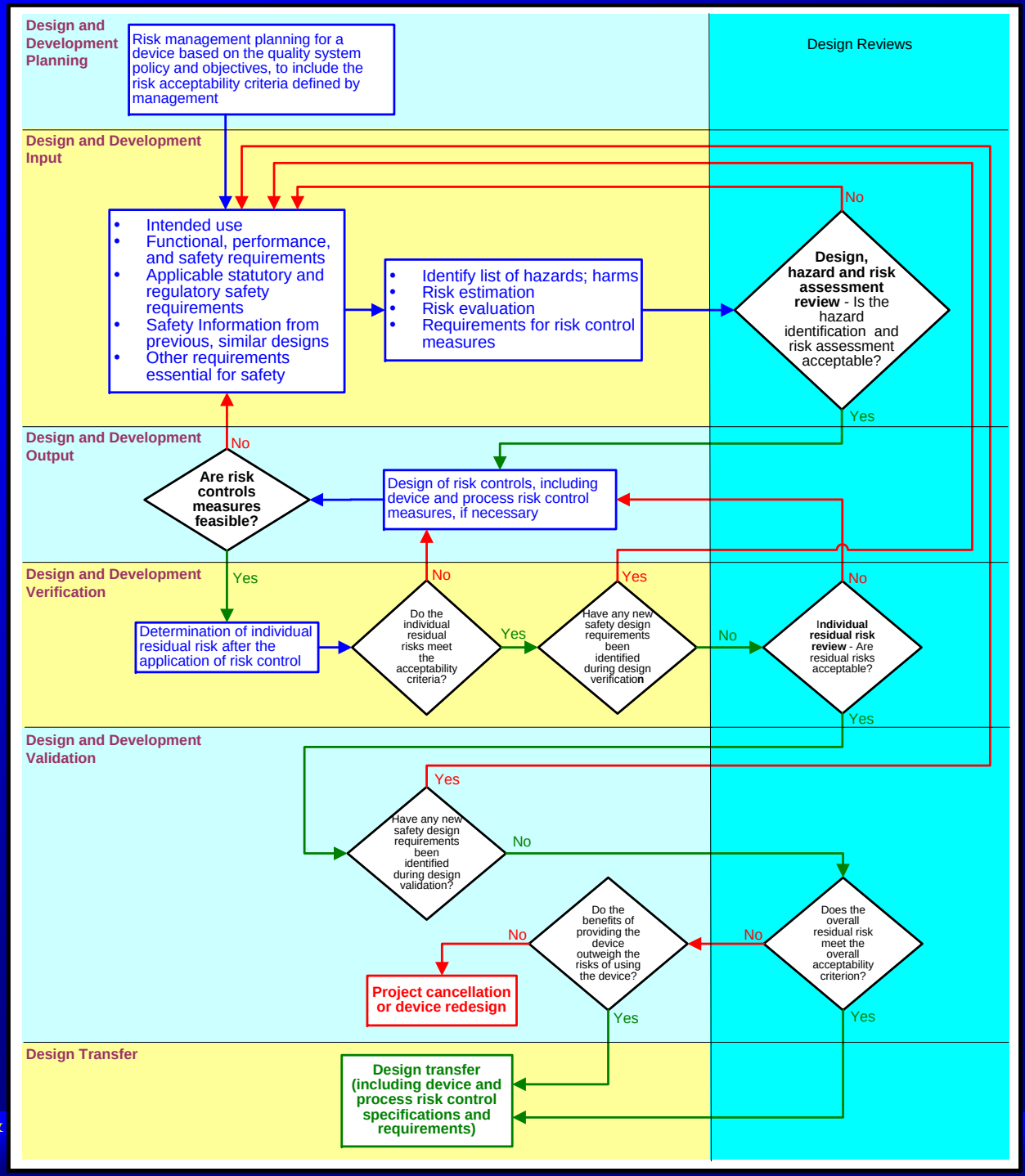
- If, at any time, a risk is determined to be unacceptable, part or all of the existing risk analysis should be re-examined and appropriate action taken to meet the established risk acceptability criteria.
- If a new hazard is identified, all four phases of risk management should be performed.

Risk Management In Design Controls

- **Identify hazards, develop a hazards list**
- **Determine the source of the hazard (any combination of product design, manufacturing, user)**
- **Analyze the hazard using appropriate tools (FTA, FMEA, HACCP, Human Factors Analysis, etc.)**

Risk Management In Design Controls

- **Minimize risks (redesign, process validation or process variability reduction, labeling, user education, etc.)**
- **Determine the overall or total risk from all sources**
- **Determine risk acceptability as a part of the completed design validation**


Design and Development Planning
Risk management planning for a device based on the quality system policy and objectives, to include the risk acceptability criteria defined by management
Design Reviews
Design and Development Input
Intended use
Functional, performance, and safety requirements
Applicable statutory and regulatory safety requirements
Safety Information from previous, similar designs
Other requirements essential for safety
Identify list of hazards; harms
Risk estimation
Risk evaluation
Requirements for risk control measures
Design, hazard and risk assessment review - Is the hazard identification and risk assessment acceptable?
No
Yes
Design and Development Output
Are risk controls measures feasible?
No
Design of risk controls, including device and process risk control measures, if necessary
Design and Development Verification
Yes
Determination of individual residual risk after the application of risk control
Do the individual residual risks meet the acceptability criteria?
No
Yes
Have any new safety design requirements been identified during design verification
Yes
No
Individual residual risk review - Are residual risks acceptable?
No
Yes
Design and Development Validation
Have any new safety design requirements been identified during design validation?
Yes
No
Do the benefits of providing the device outweigh the risks of using the device?
No
Project cancellation or device redesign
Does the overall residual risk meet the overall acceptability criterion?
No
Yes
Yes
Design Transfer
Design transfer (including device and process risk control specifications and requirements)

Risk Management In The Quality System

- Risk Management decisions and documentation from design and development becomes a living and ever changing design input as experience and post market feedback occurs!

Risk Management In The Quality System

- Risk Management needs to be procedurally tied into:
  - Design Controls
  - Purchasing procedures and criteria
  - Acceptance Activity procedures and criteria
  - Manufacturing activities
  - Process validations
  - Rework procedures and decisions
  - Corrective and preventive actions

Risk Management Principles and Activities Within a Quality Management System

Case Study

Temporomandibular Joint (TMJ) Implants

Temporomandibular Joint (TMJ)

The TMJ is comparable to a ball-in-socket joint.

The ball (condyle) is a part of the lower jaw (mandible).

The socket (fossa) is part of the skull.

These two parts come together to form the moveable joint, which can be felt when placing fingers over the skin in front of the ears while opening and closing the mouth.

TMJ Implants

In March 1983, a company began marketing a Interpositional Implant (IPI) to treat TMJ problems. The firm claimed substantial equivalence to an existing product, silicone sheeting, which was also used as a TMJ implant.

Both products included Teflon as key components.

TMJ Implants

Warnings against the use of Teflon in these type of applications date back to 1963 and 1974

Study published in 1984 concludes Proplast coating (consisting of Teflon) has insufficient strength.

Subsequent studies published in 1986 raise further concerns regarding the use of teflon in these applications.

TMJ Implants

Patients and physicians began reporting problems, including:

- **severe pain around the ear and in the jaw area**
- **radiographic evidence of severe bone loss to the condyle and glenoid fossa**
- **limited lower jaw movement**
- **bone degeneration/soft tissue deterioration**
- **joint noise in the jaw**
- **nausea, dizziness or ringing in the ear**
- **fragmentation and/or displacement of the implant**
- **infection**
- **vision and hearing problems**

TMJ Implants

Complaints in conjunction with data published earlier led to these implants being taken off the market.

TMJ Implants

Could this have been avoided or prevented under current approach to Risk Management?

As discussed in previous slides….

- The degree to which safety considerations are addressed should be ***commensurate with the degree of the risk***, ***the nature of the device*** and ***the benefit to the patient***.

Use of teflon in joint replacement was known to be problematic as early as 1963 – further research appears to have been indicated before starting production or placing on the market.

Determination of acceptable levels of risk:

Known issues and published concerns regarding the use of teflon based materials in implants were not properly recognized during the development period.

Risk analysis

Known and published general hazards were not properly recognized

- **Intense "foreign body" reactions**
- **Insufficient strength to withstand normal weight-bearing loads**
- **Deterioration of bone and tissue**
- **Intended as a long-term implant?**

Risk estimation

Overall activity appears to have been incomplete!

Certain aspects not included in the Risk Analysis may have easily been ….

For example:

- **Adverse tissue reactions caused by *wear debris* (concern published in 1963)**
- **silicone rubber and Teflon-Proplast are not biologically acceptable implant materials in the functional TMJ (study published 1989)**
- **Results of laboratory tests on IPIs (published in 1992) showed a service life of about three years. Intermediate and long-term survival of implant was uncertain.**

Determination of risk reduction measures:

Since not all risks were properly identified, risk reduction measures were not identified for key aspects!

- **Package insert states "Prognosis for the implant's success beyond 3 years was unknown"**

Risk control and monitoring activities

Risk control measures taken by the firm as a result of post market information were limited to:

1988 – product distribution suspended

1990 – Company issues advisory letter to physicians

This is a case where risk management:

- **might have helped determine that teflon was not an appropriate material for TMJ implants.**
- **might have helped the company recognize the problem with the product sooner, before thousands of patients received the implants.**

Thank you on behalf of Study Group 3 and the GHTF for your time and attention.

Questions?

APPENDIX

Definitions

- **Harm**
  - physical injury or damage to the health of people, or damage to property or the environment [ISO/IEC Guide 51:1999, definition 3.1]
- **Hazard**
  - potential source of harm [ISO/IEC Guide 51:1999, definition 3.5]
- **Residual Risk**
  - risk remaining after protective measures have been taken [ISO/IEC Guide 51:1999, definition 3.9]
- **Risk**
  - combination of the probability of occurrence of harm and the severity of that harm [ISO/IEC Guide 51:1999, definition 3.2]

Definitions

- **Risk Analysis**
  - systematic use of available information to identify hazards and to estimate the risk [ISO/IEC Guide 51:1999, definition 3.10]
- **Risk Assessment**
  - overall process comprising a risk analysis and a risk evaluation [ISO/IEC Guide 51:1999, definition 3.12]
- **Risk Control**
  - process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels [ISO 14971:2000, definition 2.16]

Definitions

- **Risk Evaluation**
  - judgment, on the basis of risk analysis, of whether a risk which is acceptable has been achieved in a given context based on the current values of society [NOTE Based on ISO/IEC Guide 51: 1999, definitions 3.11 and 3.7]
- **Risk Management**
  - systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating and controlling risk [ISO 14971:2000, definition 2.18]

Process Validation Guidance

GHTF/SG3/N99-10:2004

4th APEC-Funded Seminar on
Harmonization of Medical Device Regulation
Kuala Lumpur
March 5-7, 2008

Gunter Frey
Vice Chair SG3

Introduction

- Purpose & Scope of SG3/N99
- What is process validation?
- How are processes validated?
- What processes must be validated?
- How to maintain state of validation
- Revalidation

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

1.1 Purpose

- To assist manufacturers in understanding quality management system requirements concerning process validation

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

1.2 Scope

- Applicable to manufacturing, servicing and installation processes for medical devices
- Does not cover verification of design output or design validation

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

2.4 Process Validation (Definition)

- Establishing by *objective evidence* that a process *consistently* produces a result or product meeting its *predetermined requirements*.

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

2.6 Verification (Definition)

- Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Three Elements of Process Validation

- Verify that equipment is installed and operating properly *(Installation Qualification -IQ)*
- Develop process that can produce product or result that meets all specifications *(Operational Qualification - OQ)*
- Verify that process can produce product or result that meets all specifications consistently over time *(Performance Qualification - PQ)*

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Steps in Validating a Process

- Develop validation protocol
- Conduct installation qualification
- Conduct operational qualification
- Conduct performance qualification
- Analyze results and reach conclusions

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Validation Protocol

- A document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.
- Criteria for revalidation and extent of revalidation (complete or partial)

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Installation Qualification (IQ)

- Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Some IQ Considerations

- Equipment manufacturer's recommendations
- Electricity: supply, reliability
- Water: supply, pressure, quality
- Air: pressure, quality
- Calibration: schedule, documentation
- Maintenance: schedule, procedures, documentation, spare parts

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Operational Qualification (OQ)

- Establishing by *objective evidence* process control limits and *action levels* which result in product that meets *all* predetermined requirements.

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Some OQ Considerations

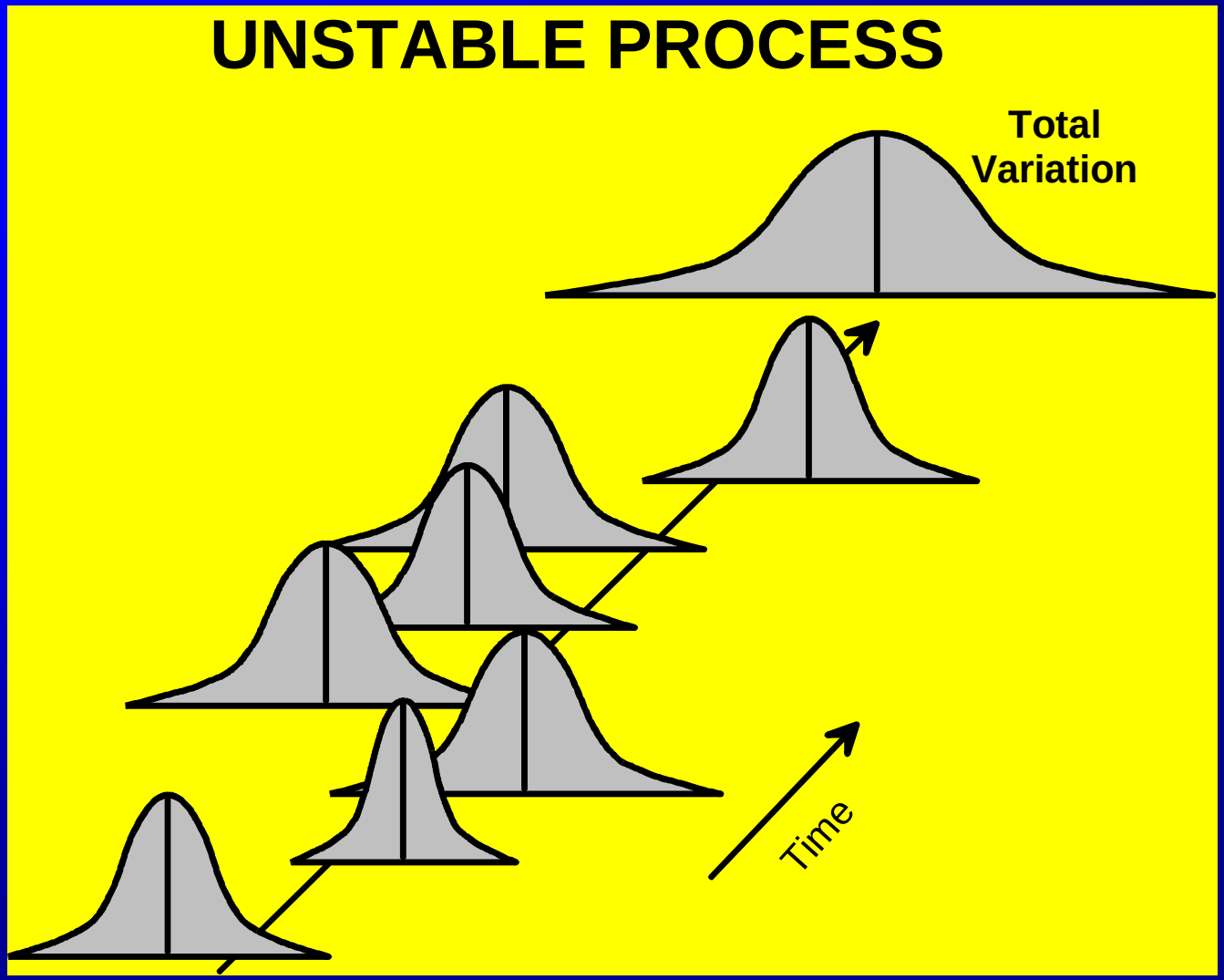
- Things that should be Established:
  - Procedure
  - Process control limits
  - Output specifications
  - Alert levels and action levels
  - Specifications for components, manufacturing materials
- Environmental conditions that may affect process stability
  - Temperature
  - Humidity
  - Light
  - Particle count, contamination
  - Other

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

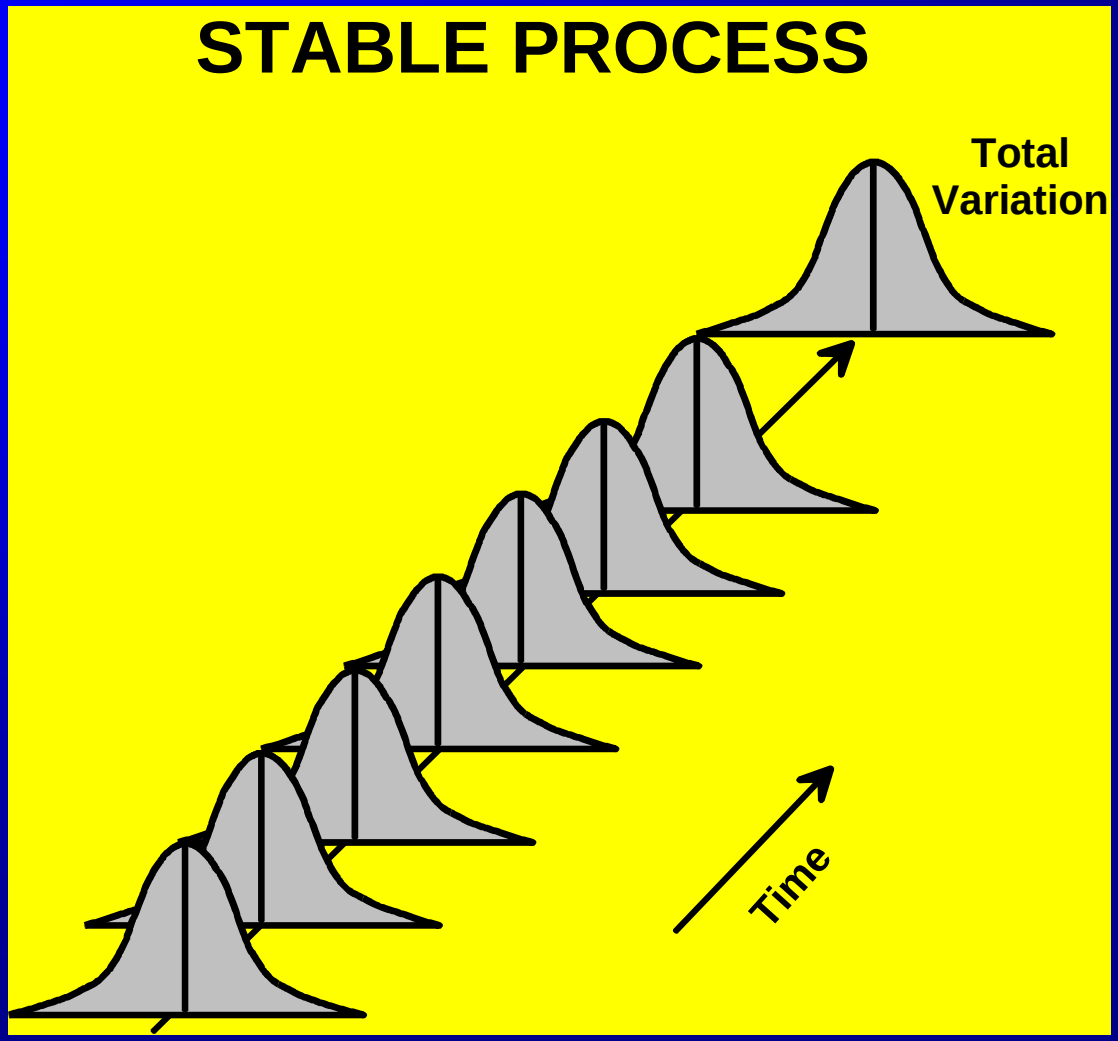
Performance Qualification (PQ)

- Establishing by objective evidence that the process, under *anticipated conditions*, *consistently* produces a product which meets *all* predetermined requirements

UNSTABLE PROCESS



STABLE PROCESS



SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Monitor and control process

- Purpose: to ensure process remains within established parameters under anticipated conditions
- Investigate deviations from established parameters
- Take corrective action
- Consider whether revalidation is necessary

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Changes in process or product

- Evaluate changes in process, product, procedures, equipment, personnel, environment, etc. to determine effect of change
- Is revalidation necessary?
- How much revalidation is necessary to assure process is capable and stable?

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Periodic revalidation

- Consider periodic revalidation where *cumulative* minor changes to process and raw materials may eventually affect process
- Sterilization processes typically are revalidated periodically (once a year or as needed) as specified in voluntary standards

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Some reasons for revalidation

- Change in process that may affect quality or validation status
- Negative trend in quality indicators
- Change in the product design that affects the process
- Process is moved within facility or transferred from one facility to another
- Change in the application of the process

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Using historical data for validation

- Validation can be partially based on accumulated historical manufacturing, testing, control and other data
- Sources of historical data:

- batch or lot records
- manufacturing log books
- test and inspection results
- control charts
- customer feedback
- field failure reports
- service reports
- audit reports
- generic feedback

SG3/N99-10 (Edition 2) Quality Management Systems - Process Validation Guidance.

Using historical data for validation

- All appropriate data must have been collected AND collected in a manner that allows adequate analysis
- Historical pass/fail manufacturing data usually is not adequate

Summary

- Key features of Process Validation Guidance GHTF/SG3/N99-10:2004
- IQ, OQ, and PQ

GHTF SG3 Training Summary

1. **GHTF SG3 – Role, Members, Documents**
2. **Quality Management Systems: History and Evolution**
3. **ISO13485:2003 - An Overview**
4. **Risk Management Principles and Activities Within a Quality Management System**
5. **Process Validation**

END

Regulatory Links & Sources of Standards

Additional information

European Medical Device Directive 93/42/EEC:
http://ec.europa.eu/enterprise/medical_devices/guide-stds-directives/cons_vers_93-42-eec.pdf

European Medical Device Directive Guidance documents:
http://www.meddev.info

Canadian Medical Devices Regulations:
http://laws.justice.gc.ca/en/f-27/sor-98-282/126598.html

Australian Medical Devices Regulations:
http://scaleplus.law.gov.au/html/pastereg/3/1762/top.htm

Global Harmonization Task Force:
http://www.ghtf.org

Japan MHLW:
http://www.mhlw.go.jp/english/index.html

China:

CNCA: http://www.cnca.gov.cn/index.htm or http://www.cnca.gov.cn/download/english.html
SFDA: http://www.sfda.gov.cn/eng/

Additional information (cont.):

FDA:

General:
http://www.fda.gov

FDA site searchable for QSR and Electronic Records & Signature (21 CFR Parts 820 and 11) :
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

FDA Guidance documents
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfGGP/Search.cfm

Additional information (cont.)

Guidance on Technical Files developed by the Co-ordination of Notified Bodies - Medical Devices (NB-MED) can be found at:
http://www.meddev.info/_documents/R2_5_1-5_rev4.pdf

Guidance on "Essential Principles of Safety and Performance of Medical Devices on a Global Basis" developed by Study Group 1 of the Global Harmonization Task Force can be found at:
http://www.ghtf.org/sg1/inventorysg1/sg1-n20r5.pdf

Sources of Standards - IEC

The International Electrotechnical Commission (IEC) is the leading global organization that prepares and publishes international standards for all electrical, electronic and related technologies.

International Electromedical Commission (IEC)

Central Office of the IEC

3, rue de Varembe

P.O. Box 131

CH-1211 Geneva 20

Switzerland

Telephone: (+41) 22 919 02 11

Fax: (+41) 22 919 03 00

Web Site: http://www.iec.ch

Sources of Standards - ISO

ISO is a non-governmental organization, consisting of a network of the national standards institutes of 148 countries, on the basis of one member per country, with a Central Secretariat in Geneva, Switzerland, that coordinates the system

International Organization for Standardization (ISO)

1, rue de Varembe

Case postale 56

CH-1211 Geneve 20

Switzerland

Telephone: (+41) 22 749 01 11

Fax: (+41) 22 733 34 30

e-mail: central@iso.ch

Web Site: http://www.iso.ch

Sources of Standards - CEN

CEN, the European Committee for Standardization, develops voluntary technical standards which promote free trade, the safety of workers and consumers, interoperability of networks, environmental protection, exploitation of research and development programs, and public procurement.

European Committee for Standardization (CEN)

Rue de Stassart, 36

B-1050 Brussels

Belgium

Telephone: (+32) 2 550 08 11

Fax: (+32) 2 550 08 19

E-Mail: infodesk@cenorm.be

Web Site: http://www.cenorm.be/cenorm/index.htm

Sources of Standards - CENELEC

CENELEC is a non-profit technical organization set up under Belgian law and composed of the National Electrotechnical Committees of 28 European countries. CENELEC prepares voluntary electrotechnical standards.

Comite Europeene de Normalisation Electrotechnique (CENELEC)
Rue de Stassart, 35
B-1050 Brussels
Belgium
Telephone: (+32) 2 519 68 71
Fax: (+32) 2 519 69 19
E-Mail: info@cenelec.org
Web Site: http://www.cenelec.org

Sources of Standards - ASTM

ASTM International develops voluntary technical standards for materials, products, systems, and services.

American Society for Testing and Materials (ASTM)
100 Barr Harbor Drive
West Conshohocken, PA, 19428-2959
USA
Telephone: (610) 832-9500
Fax: (610) 832-9555
Web Site: http://www.astm.org

Sources of Standards - ANSI

The American National Standards Institute (ANSI) is a private, non-profit organization (501(c)3) that administers and coordinates the U.S. voluntary standardization and conformity assessment system.

American National Standards Institute (ANSI)
1819 L Street, NW, Suite 600
Washington, DC 20036
USA
Telephone: (202) 293-8020
Fax: (202) 293-9287
Web Site: http://www.ansi.org

Sources of Standards - AAMI

The AAMI standards program consists of over 100 technical committees and working groups that produce Standards, Recommended Practices, and Technical Information Reports for medical devices.

Association for the Advancement of Medical Instrumentation (AAMI)

1110 North Glebe Road, Suite 220

Arlington, VA 22201-4795

USA

Telephone: (703) 525-4890

Fax: (703) 276-0793

Web Site: http://www.aami.org

Sources of Standards - NEMA

NEMA provides a forum for the standardization of electrical equipment and develops technical standards.

National Electrical Manufacturers Association (NEMA)
1300 N. 17th Street, Suite 1847
Rosslyn, VA, 22209
USA

Telephone:	(703) 841-3200
Fax:	(703) 841-5900
E-Mail:	webmaster@nema.org
Web Site:	http://www.nema.org

Sources of Standards - UL

Underwriters Laboratories Inc. (UL) is an independent, not-for-profit product-safety testing and certification organization, as well as a developer of safety standards

Underwriters Laboratories, Inc.
333 Pfingsten Road
Northbrook, IL 60062-2096
USA
Telephone: (847) 272-8800
Fax: (847) 272-8129
E-mail: northbrook@us.ul.com
Web Site: http://www.ul.com

Sources of Standards - CNCA

Certification Accreditation Administration Of The People's Republic Of China (CNCA)

9A Madian Street

Haidian District

Beijing 100088

China

Telephone: (+86) 10 - 82260766 or 82262775

Fax: (+86) 10 - 82260767

E-Mail: webmaster@cnca.gov.cn

Web Site: http://www.cnca.gov.cn

Sources of Standards - JISC

JISC consists of many national committees and plays a central role in standardization activities in Japan.

Japanese Industrial Standards Committee (JISC)
1-3-1 Kasumigaseki
Chiyoda-ku
Tokyo 100-8901
Japan
Telephone: +81-3-3501-9471
Fax: +81-3-3580-8637
E-Mail: jisc@meti.go.jp
Web Site: http://www.jisc.go.jp/eng/

SG1 – Practical Implementation of Harmonised Guidelines

6 March 2008

Health Sciences Authority • To be the leading innovative authority protecting and advancing national health and safety

Centre for Medical Device Regulation
Health Products Regulation Group
Health Sciences Authority

SG1 Guidances

SG1 Guidances: finalised guidances
draft guidances

Examples: Definition of medical devices
Classification rules
Essential principles
Conformity assessment

Guidance – Is it the Solution?

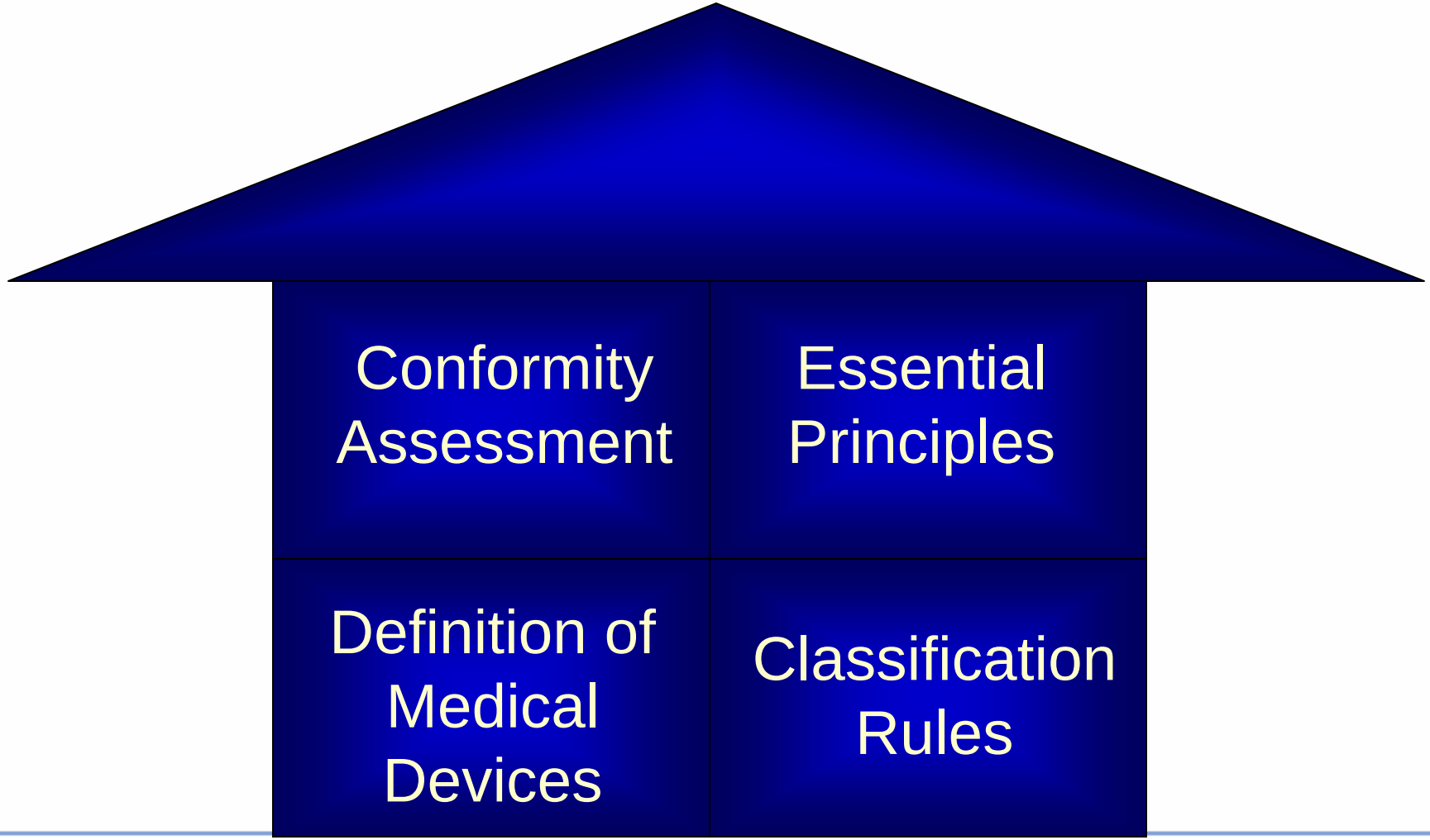
Panacea (cure-all / universal remedy)

OR

Pandora's Box

How do we make sure it becomes the **solution?**

Making Sense of Guidances – Piecing the Pieces Together



Legal Status of Guidances

	Enforceable?	Non-Enforceable?
Definition of medical device	Adopt entire document? Redraft?	Can you include it in your regulations?
Classification rules	Adopt entire document? Redraft? (difficult task)	Can you include it without redrafting by your lawyers into your regulations?
Essential Principles	Is it written in the language and style that your population understands?	Can you include it without redrafting by your lawyers into your regulations?

Elements Of Conformity Assessment

Elements regulatory authorities may include in a conformity assessment system are:-

(A) Conformity assessment of the quality management system:

1. a quality management system;
2. a system for post-market surveillance;

(B) Conformity assessment of device safety and performance:

3. summary technical documentation;
4. a declaration of conformity;

(C) Registration:

5. the registration of manufacturers and their medical devices by the regulatory authority.

Elements Of Conformity Assessment

Element	Description	Benefits
1	A quality management system	Emphasises that quality must be built into the device during the design and the production stage, as well as maintaining it throughout the entire product life cycle.

Elements Of Conformity Assessment

Element	Description	Benefits
2	A system for post-market surveillance	To ensure the continued safety and performance of a device after it is placed on the local market. The obligation is on the manufacturers and its local authorised representative to have an effective post market surveillance system in place

Elements Of Conformity Assessment

Element	Description	Benefits
3	Summary Technical Documentation	Provides summarised technical data

Elements Of Conformity Assessment

Element	Description	Benefits
4	A Declaration of Conformity	Provides a legal basis and assurance when the manufacturer, or its local authorised representative, makes a declaration (for eg. that a device product is tested to an international standard) that it meets the local regulatory requirements.

Elements Of Conformity Assessment

Elemt	Description	Benefits
5	The registration of manufacturers and their Medical Devices by the regulatory authority	In essence, to allow regulatory authorities to know “who” is selling “what” in their local markets. This is especially important for effective enforcement of local medical device regulations.

Risk Management

- What is your risk management framework?
- What are the obligations of the manufacturers, importers, distributors, 3rd party certification bodies, 3rd party conformity assessment bodies, 3rd party logistics companies, clinical trial organisations?

Local Requirements

- Understanding local and international obligations (e.g. WTO obligations)
- Local trading models and scenarios
- Understanding local requirements (risk appetite)
- Adaptation to local requirements
- Industry feedback
- Avoiding past mistakes of others through sharing

Conclusion

- SG1 guidances
- Are they the cure-all / universal remedy?
- Legal status of guidances
- Risk management framework
- Local requirements

- **Many questions seeking answers**
- **They must be answered before effective and practical**

IMPLEMENTATION

Thank You

Health Sciences Authority • To be the leading innovative authority protecting and advancing national health and safety

Centre for Medical Device Regulation
Health Products Regulation Group
Health Sciences Authority

Definition of Manufacturer

John Brennan
European Commission

Definition of Manufacturer

Why is GHTF looking at this?

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Why is GHTF looking at this?

- Responsibility for safety for a device
- Many have a role to play

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Why is GHTF looking at this?

- Responsibility for safety for a device
- Many have a role to play

Seller, user, maker, designer, repackager, importer, distributor, regulator, servicing, repair, assembler, clinician, etc.

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Define the players

So you need to define the players

It has to be clear who you are talking about

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Responsibilities

And why do you have to be clear who you are talking about?

Because you will later assign (legal) responsibilities and tasks

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Key Players

Looking at our systems key players are identified:

- Manufacturer
- Authorised Representative
- Distributor
- Importer

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Manufacturer

The Regulator wants to establish easily the one person who takes regulatory responsibility for a medical device that is marketed within its jurisdiction.

Not as easy as you think?

Maker, designer, steriliser, marketer, distributor, logo, final assembler, corporate entity, national sponsor, refurbishing, etc.

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Manufacturer

Finally linked it to the name on the device, that is, what the consumer (the user) sees

"Manufacturer" means any natural or legal person who designs and/or manufactures a medical device with the intention of making the finished medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by a third party(ies)

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Other Players

"Authorised Representative" means any natural or legal person established within a country or jurisdiction who has received a mandate from the manufacturer to act on his behalf for specific tasks with regard to the latter's obligations under that country or jurisdiction's legislation

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Other Players

"Distributor" means any natural or legal person in the supply chain who, on his own behalf, furthers the availability of a medical device to the end user

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Other Players

"Importer" means any natural or legal person in the supply chain who first makes a medical device, manufactured in another jurisdiction, available in a country or jurisdiction where it is to be marketed

- Why is GHTF looking at this?
- Define the Players?
- Responsibilities
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Experience in Europe

Problems

Manufacturer	OBL Virtual Manufacturing Reprocessing
Authorised Representative	One or more per manufacturer One or more per device What is their exact responsibility
Distributor	Barely mentioned in the text But has a significant role
Importer	Lost in our text Effectively no responsibility

- Why is GHTF looking at this?
- Define the Players?
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Definition of Manufacturer

Thank You For Listening

- Why is GHTF looking at this?
- Define the Players?
- Key Players
- Manufacturer
- Other Players
- Experience in Europe

Global Harmonization Task Force

Study Group 4 – "Regulatory Auditing"

Regulatory Auditing Strategy

Tim Missios, Vice Chair GHTF SG4**,**

Purpose of Study Group SG4

SG4 has been charged with the task of examining quality system auditing practices (initially among the founding members of the GHTF) and developing guidance documents laying harmonized principles for the medical device auditing process

Goals of GHTF SG 4

- Provide guidance for regulatory auditing of medical device manufacturers' quality systems
- Improve the effectiveness of regulatory audits
- Promote greater uniformity in the way regulatory bodies throughout the world conduct audits

SG 4 Current Membership

Active members consist of representatives from all founding members

CAs, CABs and industry representatives are present from Australia, Canada, Europe, Japan Taiwan and USA.

Chair of GHTF-SG 4 is Markus Zobrist – Swiss Medic

Secretary: Jan Welch – FDA

Vice chair: Tim Missios – Canadian Industry, MEDEC, Boston Scientific

New US Industry Member

SG 4 Current Membership

- U.S. (3)
  - Regulatory (2- **Secretary**)
  - Industry (1)
- Canada (2)
  - Regulatory (1)
  - Industry (1- **Vice Chair**)
- Australia (1)
  - Regulatory (1)
- Europe (7)
  - Regulatory (2 – **SG4 Chair**)
  - Notified Bodies (2)
  - Industry (3)
- Japan (4)
  - Regulatory (3)
  - Industry (1)

Structure of GHTF-SG4 "Regulatory Auditing" Documents

SG4 has developed / is developing a set of guidance documents dealing with:

Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers

– Part 1: General Requirements **(Status: Final)** + 4 Supplements **(Status: Final)**
– Part 2: Regulatory Auditing Strategy **(Status: Final)**
– Part 3: Regulatory Audit Reports **(Status: Final)**

Seven Final Guidance Documents developed by SG4

SG 4 Final Guidance

SG4(99) 28

Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers

Part 1: General Requirements

(updated Comment Period May 14, 2008)

General Requirements

- Written for auditing organizations
- May also be useful for manufacturers
- Provides guidance for establishing, planning, carrying out and documenting regulatory audits of quality systems
- Describes competence criteria for the audit team

SG 4 Final Guidance

SG 4(99) 14

Part 1: General Requirements

Supplement 1

Audit Language Requirements

Audit Language Requirements

- Purpose: To assure that auditors and the auditee are able to communicate clearly during an audit
- Before the audit, determine if auditors and auditee have a common language
- Arrange for an interpreter if there is no common language

SG 4 Final Guidance

SG4(00) 3

Part 1: General Requirements

Supplement 2

Training Requirements for Auditors

Training Requirements for Auditors

- The document describes training elements required to:
  - Prepare an individual to be an auditor
  - Qualify auditors to conduct regulatory audits of medical device manufacturers' quality systems
  - Maintain auditor qualifications

SG 4 Final Guidance

SG4 N(99) 24R3:

Part 1: General Requirements

Supplement No. 4

Compilation of Audit Documentation

Compilation of Audit Documentation

- Provides guidelines for compiling audit documentation within auditing organization for internal use
- This document does not address the exchange of audit documentation between auditing organizations

SG 4 Final Guidance

SG4-N26R1:2001

Part 1: General Requirements

Supplement No. 6

Observed Audits of Conformity Assessment Bodies

Observed Audits of Conformity Assessment Bodies

- Sets out guidance for observing audits conducted by Conformity Assessment Bodies (CABs).
- Observing audits enables a regulatory authority to evaluate the adequacy of the CAB's audits

SG 4 Final Guidance

SG4/N30 R 20: 2006

Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers

Part 2:

Regulatory Auditing Strategy

Regulatory Auditing Strategy

- Provides guidance on how to audit the effectiveness of quality systems in a systematic and effective manner within a reasonable time
- Purpose is to promote audit consistency – a necessity for harmonization and mutual recognition of audit results.

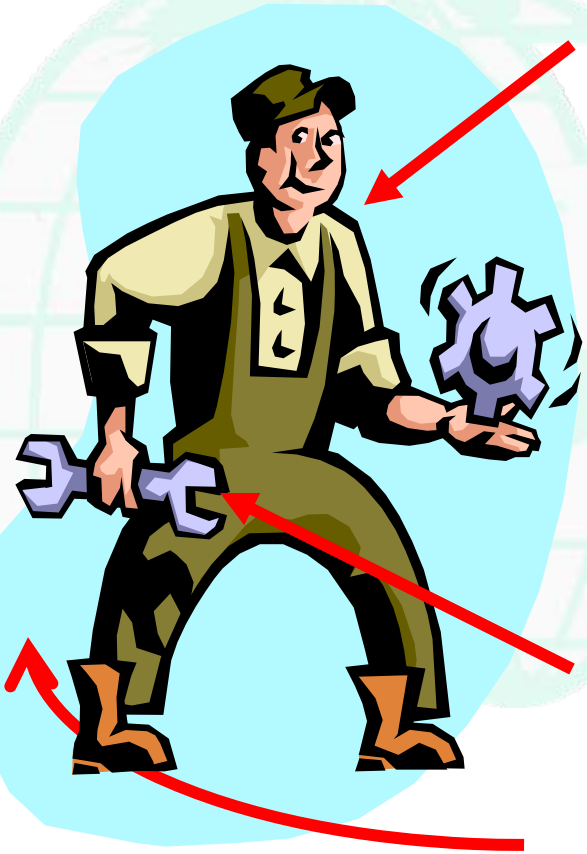
Topics

1. Does the process work?
2. How to demonstrate proper audit coverage?
3. Is Risk Management in place?
4. Conclusions

1. Does the process work

…according to the requirements of ISO 13485:2003 (QMS MEDICAL DEVICES)

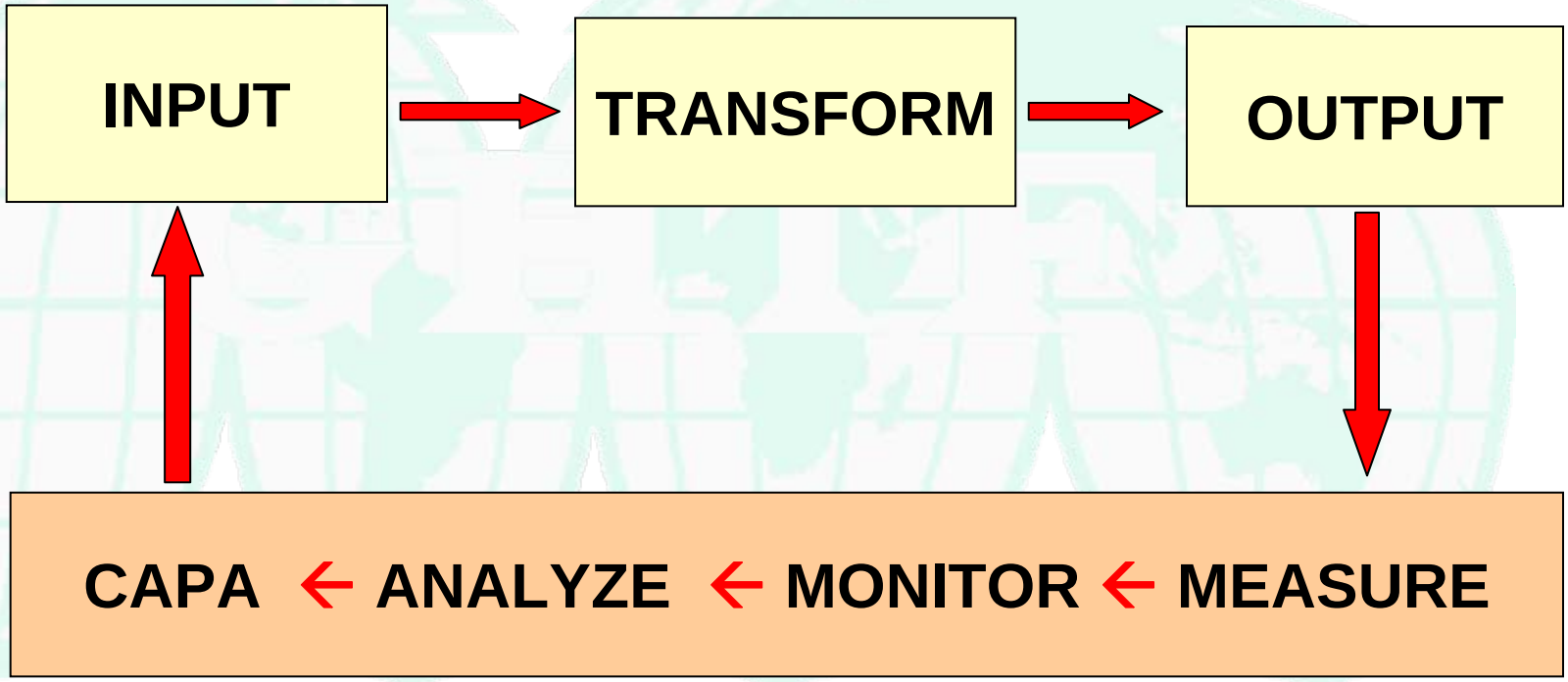
Attributes of a Process



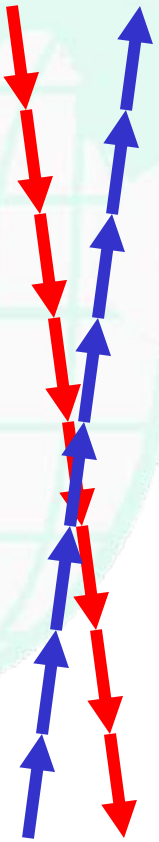
- PEOPLE
- METHODS
- MATERIALS
- MEASURES
- EQUIPMENT
- ENVIRONMENT

JW2E Development Method

Process Cycle



Process interactions

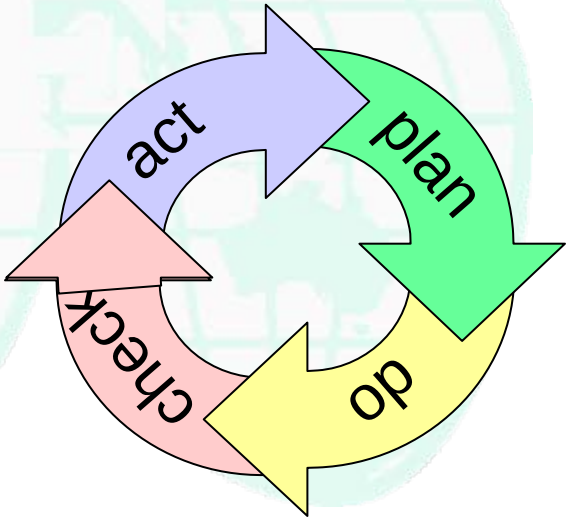


1. Management
2. Design and development
3. Product documentation
4. Production and process controls
5. Corrective and preventive actions
6. Purchasing controls
7. Documentation and records
8. Customer related processes

Process under control

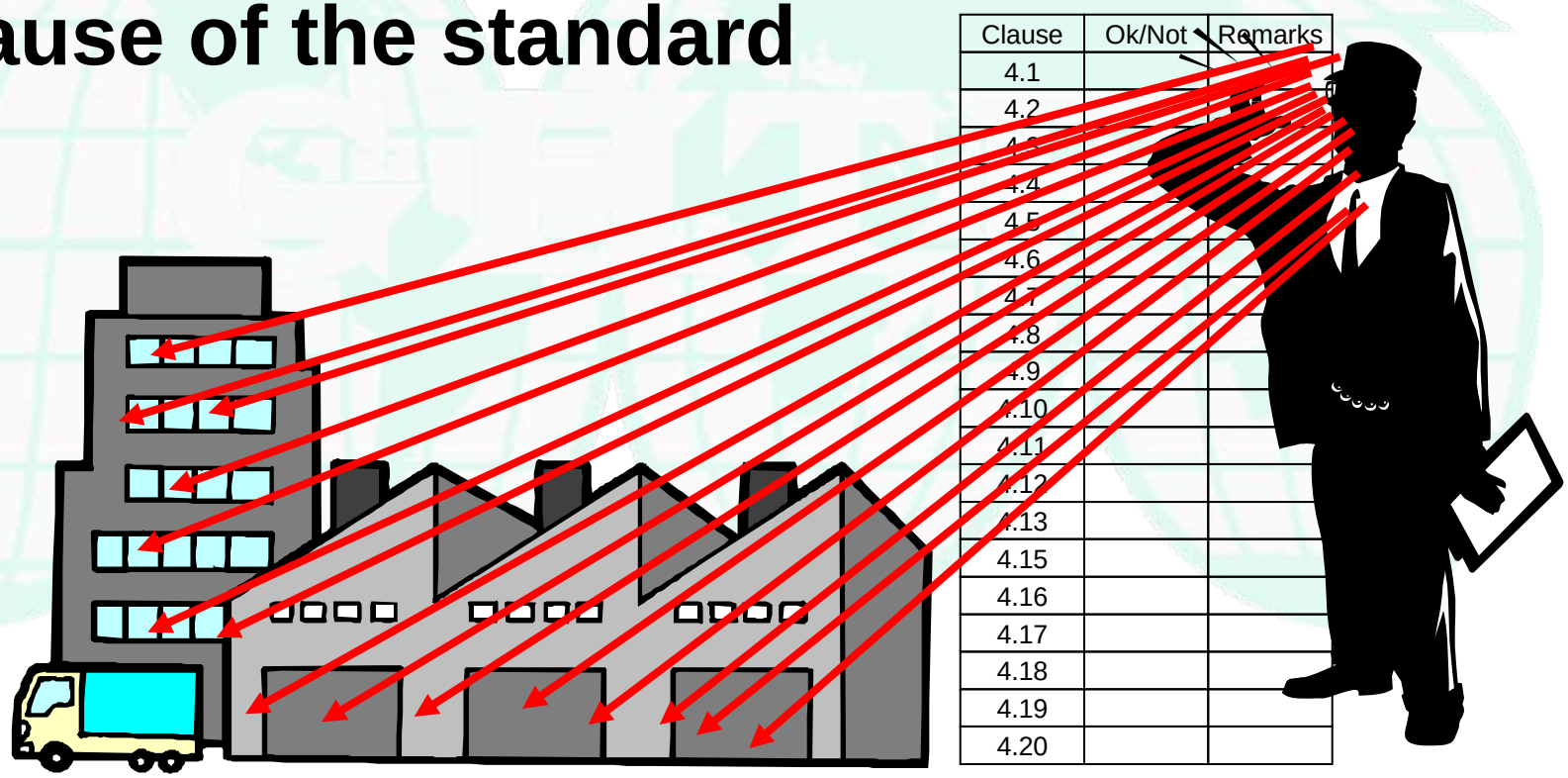
The process is unter control when the activity is

- Planned,
- Implemented,
- Measured &
- Action is taken!



2. How to demonstrate proper audit coverage

Good auditing practice in the past: Use of a checklist listing each individual clause of the standard

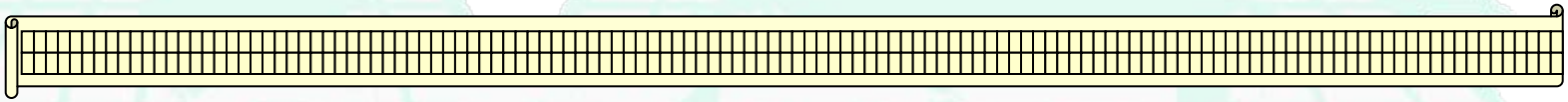


Audit challenge is increased: ISO13485:2003 – has 43 clauses!

- 7.5
  - 7.5.1
    - 7.5.1.1
    - 7.5.1.2
      - 7.5.1.2.1
      - 7.5.1.2.2
      - 7.5.1.2.3
    - 7.5.1.3
  - 7.5.2

The dilemma

- Can we or should we try and demonstrate clause coverage down to the lowest level?



- Or, will full clause coverage occur naturally if we follow the manufacturers' processes?
  - How can we prove it?
  - Will the regulators believe it?

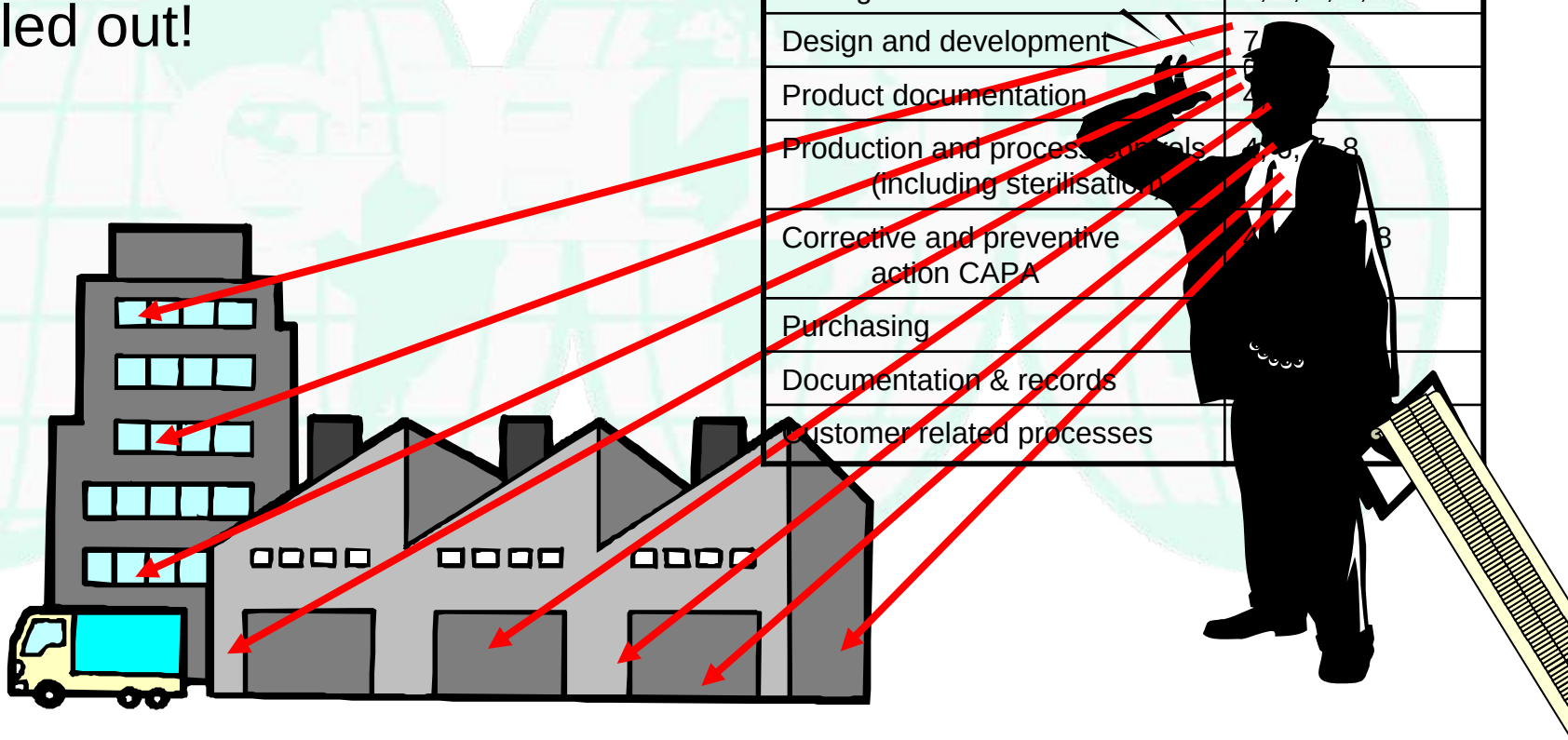
Auditing Subsystems

Subsystem	Clauses and subclauses of ISO 13485:2003
Management	4, 5, 6, 7, 8
Design and development	7
Product documentation	4, 7
Production and process controls (including sterilisation)	4, 6, 7, 8
Corrective and preventive action CAPA	4, 5, 6, 7, 8
Purchasing	7
Documentation & records	4
Customer related processes	7

State of the art is:

Use the subsystem approach for the audit even when finally a checklist needs to be filled out!

Subsystem	Clauses and subclauses of ISO 13485:2003
Management	4, 5, 6, 7, 8
Design and development	7
Product documentation	4
Production and process controls (including sterilisation)	4, 5, 7, 8
Corrective and preventive action CAPA	8
Purchasing	
Documentation & records	
Customer related processes	



3. Is Risk Management in Place

Risk Management Requirement in ISO 13485:2003

Section 7 Product realization

7.1 Planning of product realization

The organization shall establish documented requirements for risk management throughout product realization. Records arising from risk management shall be maintained.

NOTE 3 – See ISO 14971 for guidance related to risk management

Foundations

Product realization

Includes:

- Determination of customer requirements and customer communication (7.2)
- Design and development (7.3)
- Purchasing (7.4)
- Production and servicing (7.5)
- Control of monitoring and measuring devices (7.6)
- Delivery of the device

Foundations (cont'd)

ISO TIR 14969:2004

Medical devices – Quality management systems – Guidance for the application of 13485:2003

7.1.2 Risk management

Key elements of risk management include risk assessment (risk analysis and risk evaluation) and risk control

Foundations (cont'd)

Output of risk management activities can influence decisions and activities outside of product realization!

For example:

- management review decisions
- personnel training
- infrastructure
- monitoring and measurement
- handling of nonconforming product
- corrective and preventive actions
- …

Foundations (cont'd)

- **ISO 14971:2000**
  Medical devices – Application of risk management to medical devices

- **GHTF SG3 N15 R8:2005**
  Implementation of risk management principles and activities within a quality management system

Auditing a QMS

- **Risk management activities should be audited concurrently with the processes within the relevant subsystems**

- Purpose of auditing the risk management process is to ensure that adequate and effective risk management has been established and maintained through out the product realization process

- Can also assess the impact of the risk management process outputs on other areas of the QMS as mentioned in ISO TIR 14969

QMS Subsystems

1. Management
2. Design and development
3. Product documentation
4. Production and process controls
5. Corrective and preventive actions
6. Purchasing controls
7. Documentation and records
8. Customer related processes

Management Subsystem

- Verify that the product realization process incorporates risk management planning, and ongoing review of the effectiveness of risk management activities ensuring that policies, procedures, and practices are established for analyzing, evaluating and controlling risk

Management Subsystem

Auditor ...

- ☑ looks for statements in quality plan or quality manual that address the firm's approach to risk management activities
- ☑ reviews training records to determine if personnel are trained in risk management activities pertaining to their job
- ☑ determines if risk management principles are used in management reviews; are the outputs from these reviews risk-based?

Design and Development Subsystem

- Verify if products are by regulation subject to design and development procedures including risk management (e.g., hazard identification, risk evaluation and risk control)
- Verify that risk management activities are defined and implemented and that risk acceptability criteria are established and met throughout the design and development process
- Verify that any residual risk is evaluated and, where appropriate, communicated to the customer (e.g., labeling, service documents, advisory notices, etc.)
- It may be necessary to audit other subsystems to verify that risk acceptability criteria are met and residual risk is communicated if necessary

Design and Development Subsystem

- ☑Review risk analysis for a selected design project
- ☑Review design change control process procedures to determine integration of risk management principles
- ☑Select design changes for review and determine if re-evaluations were performed with respect to risk management activities

Product Documentation Subsystem

- For the product(s) selected verify that documentation includes (if required by national or regional regulations):
  - Risk management documents

☑Review technical file, design dossier, design history file, etc for this documentation

Production and Process Controls Subsystem

- Verify that the processes are controlled and monitored and operating within specified limits
- Verify that risk control measures identified by the manufacturer in production processes are controlled, monitored, and evaluated
- Verify that risk control measures are applied to delivery, installation, and servicing, where applicable
- Verify that the system for monitoring and measuring of products is adequate
- Ensure that any identified risk control measures are implemented

Production and Process Controls Subsystem

- ☑ Review validation protocol for a selected process and determine if risk management principles were used in determining key quality attributes for the process
- ☑ Determine if risk management principles were used to help establish appropriate monitoring techniques and frequencies
- ☑ Determine if risk management principles are applied to the evaluation of process changes, and the decision-making process for revalidation

Corrective and Preventive Actions Subsystem

When a CAPA results in a design change, verify that the hazard(s) and any new risks are evaluated under the risk management process.

- ☑ Are risk management principles used when deciding the scope of corrective and preventive actions? extended to similar processes or products?

- ☑ Review CAPA SOPs to determine degree of integration of risk management principles

Purchasing Controls Subsystem

Verify that the manufacturer assures the adequacy of specifications for products and services that suppliers are to provide, and defines risk management responsibilities and any necessary risk control measures

Purchasing Controls Subsystem

- ☑ Are decisions about suppliers based on risk management principles?
- ☑ Some suppliers may ship their components directly to stock, while other suppliers' components may undergo detailed acceptance activities at the manufacturer; are these differences based on risk management principles?
- ☑ Do supplier audits focus on risk management principles?

Customer Related Processes Subsystem

Confirm that customer feedback is analyzed in the product realization process and used to re-evaluate the risk assessment and, where necessary, adjust the risk management activities

- ☑ Is customer feedback evaluated in all appropriate QMS subsystems?
- ☑ Are all pertinent departments receiving the necessary information?
- ☑ Is customer feedback an input for risk management activities throughout the product realization process?

5. Conclusions

Subsystem Technique

- Regulatory auditing demands thorough and complete coverage
- Using the Subsystem technique is the current state of the art
- The Subsystem approach offers a solution to the problem of ensuring full coverage
- **and facilitates auditors to use a risk based approach for auditing**

Using the Subsystem Approach

- Leads to more efficient and effective auditing
- Leads to greater consistency in audit practices and feedback
- Increases the confidence in audit results

For benefit of

- the manufacturer
- the auditing organization
- the regulator

... and last but not least for the benefit of the patient!

SG 4 Final Guidance

SG4/N33 R 15

Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers

Part 3:

Audit Reports

Regulatory Audit Reports

- Scope
- Objectives
- User Needs of an Audit Report
- Main Points for a Regulatory Audit Report
- References for Applicable Documents

Regulatory Audit Reports

- Scope
  - used by regulators and auditing organizations as a guide for writing a report for a regulatory medical device QMS audit.
  - The regulatory audit report is a document or a set of documents from the audit team containing
    - Administrative data
    - A summary of locations
    - Functions or processes that were audited
    - Audit findings
    - Conclusions

Regulatory Audit Reports

- Objectives
  - The audit report comprises the documented evidence of a regulatory audit. It should contain sufficient information:
    - To document
      - The type of audit
      - The audit criteria
      - What was covered in the audit
      - The audit findings
    - To evaluate the manufacturer's
      - Compliance status
      - Effectiveness of the implementation of the QMS and draw audit conclusions
    - To allow for the exchange of audit reports between regulatory authorities/auditing organizations

Regulatory Audit Reports

- User Needs of an Audit Report
  - Auditing Organization/Regulator Perspective
  - Designating Authority Perspective
  - Manufacturer/Auditee Perspective

Regulatory Audit Reports

- Main points for a Regulatory Audit Report
  - The audit report is a traceable document(s) from the regulatory audit team
  - Reporting procedures should meet need of the auditing organization
  - Reporting procedures shall ensure all common data are included in their reports
  - The audit report shall be typed
  - The audit report shall be formatted so it can be stored and transferred electronically

Note: The language of the report should be agreed upon between the auditee and the auditing organization prior to the start of the audit.

Regulatory Audit Reports

- Main points for a Regulatory Audit Report
  - Data Concerning Auditee
  - Data Concerning Audit
  - Audit Trail
  - Conclusion
  - Signature and Dating of Report
  - Attachments (that could be used to support the content of the report)

Regulatory Audit Reports

- Main points for a Regulatory Audit Report – ***Signature and Dating of Report***
  - Date of the audit report
  - Lead auditor, auditor(s) names, titles and organizations
    - Signature and/or stamp of auditors on report

Regulatory Audit Reports

- References for Applicable Documents
  - GHTF/SG4/N28R2:
    - Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements (1999)
  - GHTF/SG4/N30R18:
    - Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy (final document 16 Feb 2006)
  - GHTF/SG2/N36R7:
    - Manufacturer's Trend Reporting of Adverse Events
  - US FDA 21CFR820:
    - Quality System Regulation
  - ISO 9000:2005:
    - Quality Management Systems – Fundamentals and Vocabulary
  - ISO 13485:2003:
    - Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes
  - ISO 19011:2002:
    - Guideline for Quality and/or Environmental Management Systems Auditing

Next Steps…..

Ongoing Work

SG4(PD)/N28R3

Guidelines for Regulatory Auditing of Quality Management

Systems of Medical Device Manufacturers – **Part 1: General Requirements**

Comment period until May 14, 2006

Ongoing Work

SG4 (WD)N83 - Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy, Supplement No. 1 Multi-site Audits and Audits of Suppliers

SG4 (WD)N84 - Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy, Supplement No. 2 Auditing of Supplier Control.

Next Meetings

Paris, France - April 1-3, 2008

Canada, October, 2008

Additional Information……

Visit the GHTF website at: www.ghtf.org

– Website includes
  - Steering Committee & procedure documents
  - Study group guidance documents & membership
  - Discussions from past GHTF conferences
  - Upcoming meetings and strategic plan

Thank you!

1 General details

State the proprietary name of the device and any code names assigned during device development.

Identify the manufacturer(s) of the device.

2 Description of the device and its intended application

Provide a concise physical description of the device, cross referencing to relevant sections of the manufacturer's technical information as appropriate. The description should cover information such as:

- materials, including whether it incorporates a medicinal substance (already on the market or new), tissues, or blood products;
- the device components, including software and accessories;
- mechanical characteristics; and
- others, such as sterile vs. non-sterile, radioactivity etc.

State the intended application of the device – single use/reusable; invasive/non invasive; implantable; duration of use or contact with the body; organs, tissues or body fluids contacted by the device.

Describe how the device achieves its intended purpose.

3 Intended therapeutic and/or diagnostic indications and claims

State the medical conditions to be treated, including target treatment group and diseases.

Outline any specific safety or performance claims made for the device

4 Context of the evaluation and choice of clinical data types

Outline the developmental context for the device. The information should include whether the device is based on a new technology, a new clinical application of an existing technology, or the result of incremental change of an existing technology. The amount of information will differ according to the history of the technology. Where a completely new technology has been developed, this section would need to give an overview of the developmental process and the points in the development cycle at which clinical data have been generated. For long standing technology, a shorter description of the history of the technology (with appropriate references) could be used. Clearly state if the clinical data used in the evaluation are for a comparable

device. Identify the comparable device(s) and provide a justification of the comparability, cross-referenced to the relevant non-clinical documentation that supports the claim.

State the Essential Principles relevant to the device in question, in particular, any special design features that pose special performance or safety concerns (e.g. presence of medicinal, human or animal components) that were identified in the device risk management documentation and that required assessment from a clinical perspective.

Outline how these considerations were used to choose the types of clinical data used for the evaluation. Where published scientific literature has been used, provide a brief outline of the searching/retrieval process, cross-referenced to the literature search protocol and reports.

5 Summary of the clinical data and appraisal

Provide a tabulation of the clinical data used in the evaluation, categorized according to whether the data address the performance or the safety of the device in question. (Note: many individual data sets will address both safety and performance.) Within each category, order the data according to the importance of their contribution to establishing the safety and performance of the device and in relation to any specific claims about performance or safety. Additionally, provide a brief outline of the data appraisal methods used in the evaluation, including any weighting criteria, and a summary of the key results.

Include full citations for literature-based data and the titles and investigation codes (if relevant) of any clinical investigation reports.

Cross-reference the entry for each piece of data to its location in the manufacturer's technical documentation.

6 Data analysis

6.1 **Performance**

Provide a description of the analysis used to assess performance.

Identify the datasets that are considered to be the most important in contributing to the demonstration of the overall performance of the device and, where useful, particular performance characteristics. Outline why they are considered to be "pivotal" and how they demonstrate the performance of the device collectively (e.g. consistency of results, statistical significance, clinically significance of effects).

6.2 Safety

Describe the total experience with the device, including numbers and characteristics of patients exposed to the device; and duration of follow-up of device recipients.

Provide a summary of device-related adverse events, paying particular attention to serious adverse events.

Provide specific comment on whether the safety characteristics and intended purpose of the device requires training of the end-user.

6.3 Product Literature and Instructions for Use

State whether the manufacturer's proposed product literature and Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact on the use of the device.

7 Conclusions

Outline clearly the conclusions reached about the safety and performance of the device from the evaluation, with respect to the intended use of the device. State whether the risks identified in the risk management documentation have been addressed by the clinical data.

For each proposed clinical indication state whether:

- the clinical evidence demonstrates conformity with relevant Essential Principles;
- the performance and safety of the device as claimed have been established; and
- the risks associated with the use of the device are acceptable when weighed against the benefits to the patient

4th APEC-Funded Seminar on Harmonization of Medical Device Regulation

STUDY GROUP 1

Accomplishments & Future Direction

Ginette Y. Michaud, MD
Chairperson, GHTF Study Group 1

Kuala Lumpur, Malaysia
March 6, 2008

Accomplishments & Future Work

- SG 1 Mission
- SG1 Membership, Structure and Participation
- Expansion of Study Group 1
- Update on SG1 Work Plan
- Summary Comments

Study Group 1 Mission

- Production of harmonized guidelines on medical device regulatory practices
- Focused on safety & performance of medical devices
- Scope – all products that fall within definition of GHTF/SG1/N029:2005 (including IVDMDs)

Structure, membership & participation

Structure

- "Parent" Study Group 1
- IVD Medical Devices Subgroup

SG1 Leadership:

- Ginette Michaud - Chairperson
- Benny Ons - Vice-Chairperson
- Alan Kent - Secretary
- Nancy Shadeed – IVD Medical Devices Subgroup Chairperson

Structure, membership & participation

- SG1 membership is characterized by diversity:
  - market size
  - age of medical device regulatory programs
  - relative percentage of domestic versus foreign manufacturers
  - role of Notified Bodies
  - relative roles of national versus supra-national or provincial entities

Structure, membership & participation

- Participation:
  - voluntary
  - funded by individual members
  - members recognize great potential of harmonization
  - members feel constant tug between harmonization & independent progress

Structure, membership & participation

- Membership:
  - Balanced representation by regulators and industry
  - Balanced representation from each of three regions:
    - Japan and Australia
    - European Union
    - North America
  - Expansion to include non-founding members

Expansion of Study Group 1

Recognition of regional harmonization efforts in non-founding member nations:

- AHWP Common Submission Dossier Template
- ASEAN 2010 Commitment
- Translation of GHTF docs into Spanish and Portuguese

Non-founding members have:

- Record of positive contributions to SG1
- Increasing share of global production/ market

Expansion of Study Group 1

Expansion Goals of SG1

- Give greater voice to non-founding members
- Account for diversity of perspectives
- Respond to different needs among regions & nations

Expansion of Study Group 1

Expansion efforts of SG1

Joint meetings:

- SG1 & AHWP in Kyoto Feb. 2007
- SG1 & Latin American/Caribbean delegates in Washington, D.C. Oct. 2007

- In 2007: Invitation for permanent inclusion of 2 delegates each from Latin America/Caribbean and AHWP into SG1

Update on SG1 Work Plan

- The Global Regulatory Model
- Final documents
- Documents in progress
- Upcoming document revisions

The Global Regulatory Model

SG1 guidelines are key elements of global regulatory model. They:

- define “medical device”
- define “manufacturer”
- describe device classification principles
- identify essential principles of safety & performance
- identify conformity assessment elements applicable to each class of devices

SG1 Final Documents

SG1/N29:2005 *Information Document Concerning the Definition of the Term "Medical Device"*
SG1/N41:2005 *Essential Principles of Safety and Performance of Medical Devices*
SG1/N15:2006 *Principles of Medical Devices Classification*
SG1/N040:2006 *Principles of Conformity Assessment for Medical Devices*
SG1/N43:2005 *Labelling for Medical Devices*
SG1/N012 *Role of Standards in the Assessment of Medical Devices* (18 November 1999)

SG1 Documents in Progress

Document	Status/Priority	Target for completion
SG1/N011 (PD) *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles (STED)*	**Proposed for advancement as Final Document** **Priority 1**	**Final Document 2008 / Q1**
SG1(PD)/N044 *Role of Standards in the Assessment of Medical Devices*	**Proposed for advancement as Final Document** **Priority 1**	**Final Document 2008 / Q1**

SG1 Documents in Progress

Document	Status/Priority	Target for completion
SG1(WD)/N055 *The definition of the Term Manufacturer and Related Entities.*	**Working Draft, under development by SG1/SG3/SG4** **Priority 2**	**Proposed Document 2008 / Q2**
SG1(WD)/N065 *Registration of manufacturers and their medical devices by the Regulatory Authority*	**Working Draft – joint SG1/SG3/SG4 effort** **Priority 2**	**Proposed Document 2008 / Q4**

SG1- IVDMD Documents in Progress

Document	Status/Priority	Target for completion
SG1/N045 *Principles of Classification of In Vitro Diagnostic Medical Devices*	**Proposed for advancement as Final Document Priority 1**	**Final Document 2008 / Q2**
SG1/N046 *Principles of Conformity Assessment for In Vitro Diagnostic Medical Devices*	**Proposed for advancement as Final Document Priority 1**	**Final Document 2008 / Q2**
STED for Demonstrating Conformity to the Essential Principles of Safety and Performance of IVD Medical Devices.	**First working draft in preparation** Priority 2	**Proposed Document 2008/Q4**

SG1 Upcoming Document Revisions

Document	Status/Priority	Target for completion
SG1-N29:2005 *Information Document Concerning the Definition of the Term "Medical Device"*	**Revision to being in 2008** **Priority 3**	**Proposed Document 2009 / Q2**
SG1-N41:2005 *Essential Principles of Safety & Performance of Medical Devices*	**Revision to begin in 2008** **Priority 3**	**Proposed Document 2009 / Q2**
SG1-N43:2005 *Labelling for Medical Devices*	**Revision to begin in 2008** **Priority 3**	**Proposed Document 2009 / Q2**

Summary Comments

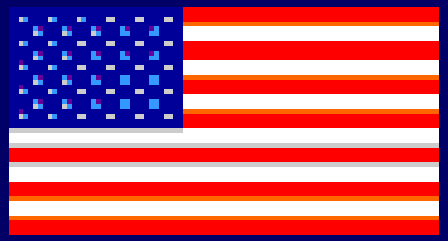
- Harmonization is *challenging work*
  - need to develop a common vision
  - obstacles posed by existing statutes & regulations
  - step-wise progress is unavoidable

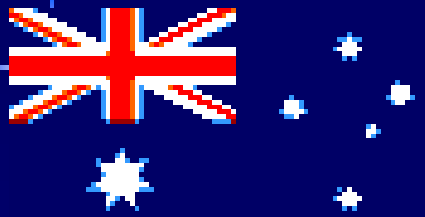
Summary Comments

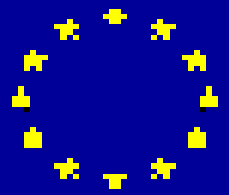
- Successful harmonization requires:
  - inclusiveness so that diverse viewpoints are considered
  - meaningful partnership between regulators & industry
  - commitment to long term goals

Summary Comments

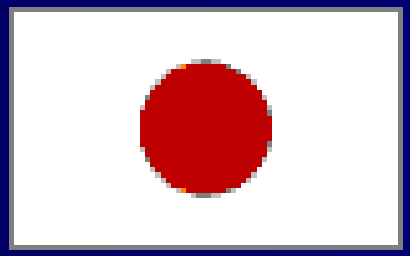
Thank you for your attention.







GHTF



Thank You …

4th APEC-Funded Seminar on Harmonization of Medical Device Regulation

STUDY GROUP 1

Accomplishments & Future Direction

Ginette Y. Michaud, MD
Chairperson, GHTF Study Group 1

Kuala Lumpur, Malaysia
March 6, 2008

Accomplishments & Future Work

- SG 1 Mission
- SG1 Membership, Structure and Participation
- Expansion of Study Group 1
- Update on SG1 Work Plan
- Summary Comments

Study Group 1 Mission

- Production of harmonized guidelines on medical device regulatory practices
- Focused on safety & performance of medical devices
- Scope – all products that fall within definition of GHTF/SG1/N029:2005 (including IVDMDs)

Structure, membership & participation

Structure

- "Parent" Study Group 1
- IVD Medical Devices Subgroup

SG1 Leadership:

- Ginette Michaud - Chairperson
- Benny Ons - Vice-Chairperson
- Alan Kent - Secretary
- Nancy Shadeed – IVD Medical Devices Subgroup Chairperson

Structure, membership & participation

- SG1 membership is characterized by diversity:
  - market size
  - age of medical device regulatory programs
  - relative percentage of domestic versus foreign manufacturers
  - role of Notified Bodies
  - relative roles of national versus supra-national or provincial entities

Structure, membership & participation

- Participation:
  - voluntary
  - funded by individual members
  - members recognize great potential of harmonization
  - members feel constant tug between harmonization & independent progress

Structure, membership & participation

- Membership:
  - Balanced representation by regulators and industry
  - Balanced representation from each of three regions:
    - Japan and Australia
    - European Union
    - North America
  - Expansion to include non-founding members

Expansion of Study Group 1

Recognition of regional harmonization efforts in non-founding member nations:

- AHWP Common Submission Dossier Template
- ASEAN 2010 Commitment
- Translation of GHTF docs into Spanish and Portuguese

Non-founding members have:

- Record of positive contributions to SG1
- Increasing share of global production/ market

Expansion of Study Group 1

Expansion Goals of SG1

- Give greater voice to non-founding members
- Account for diversity of perspectives
- Respond to different needs among regions & nations

Expansion of Study Group 1

Expansion efforts of SG1

Joint meetings:

- SG1 & AHWP in Kyoto Feb. 2007
- SG1 & Latin American/Caribbean delegates in Washington, D.C. Oct. 2007

- In 2007: Invitation for permanent inclusion of 2 delegates each from Latin America/Caribbean and AHWP into SG1

Update on SG1 Work Plan

- The Global Regulatory Model
- Final documents
- Documents in progress
- Upcoming document revisions

The Global Regulatory Model

SG1 guidelines are key elements of global regulatory model. They:

- define “medical device”
- define “manufacturer”
- describe device classification principles
- identify essential principles of safety & performance
- identify conformity assessment elements applicable to each class of devices

SG1 Final Documents

SG1/N29:2005 *Information Document Concerning the Definition of the Term "Medical Device"*
SG1/N41:2005 *Essential Principles of Safety and Performance of Medical Devices*
SG1/N15:2006 *Principles of Medical Devices Classification*
SG1/N040:2006 *Principles of Conformity Assessment for Medical Devices*
SG1/N43:2005 *Labelling for Medical Devices*
SG1/N012 *Role of Standards in the Assessment of Medical Devices* (18 November 1999)

SG1 Documents in Progress

Document	Status/Priority	Target for completion
SG1/N011 (PD) *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles (STED)*	**Proposed for advancement as Final Document** **Priority 1**	**Final Document 2008 / Q1**
SG1(PD)/N044 *Role of Standards in the Assessment of Medical Devices*	**Proposed for advancement as Final Document** **Priority 1**	**Final Document 2008 / Q1**

SG1 Documents in Progress

Document	Status/Priority	Target for completion
SG1(WD)/N055 *The definition of the Term Manufacturer and Related Entities.*	**Working Draft, under development by SG1/SG3/SG4** **Priority 2**	**Proposed Document 2008 / Q2**
SG1(WD)/N065 *Registration of manufacturers and their medical devices by the Regulatory Authority*	**Working Draft – joint SG1/SG3/SG4 effort** **Priority 2**	**Proposed Document 2008 / Q4**

SG1- IVDMD Documents in Progress

Document	Status/Priority	Target for completion
SG1/N045 *Principles of Classification of In Vitro Diagnostic Medical Devices*	**Proposed for advancement as Final Document Priority 1**	**Final Document 2008 / Q2**
SG1/N046 *Principles of Conformity Assessment for In Vitro Diagnostic Medical Devices*	**Proposed for advancement as Final Document Priority 1**	**Final Document 2008 / Q2**
STED for Demonstrating Conformity to the Essential Principles of Safety and Performance of IVD Medical Devices.	**First working draft in preparation** Priority 2	**Proposed Document 2008/Q4**

SG1 Upcoming Document Revisions

Document	Status/Priority	Target for completion
SG1-N29:2005 *Information Document Concerning the Definition of the Term "Medical Device"*	**Revision to being in 2008** **Priority 3**	**Proposed Document 2009 / Q2**
SG1-N41:2005 *Essential Principles of Safety & Performance of Medical Devices*	**Revision to begin in 2008** **Priority 3**	**Proposed Document 2009 / Q2**
SG1-N43:2005 *Labelling for Medical Devices*	**Revision to begin in 2008** **Priority 3**	**Proposed Document 2009 / Q2**

Summary Comments

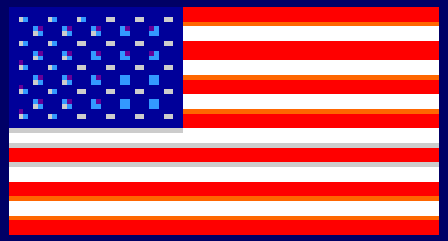
- Harmonization is *challenging work*
  - need to develop a common vision
  - obstacles posed by existing statutes & regulations
  - step-wise progress is unavoidable

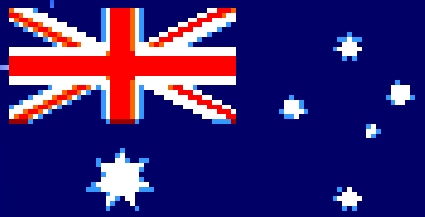
Summary Comments

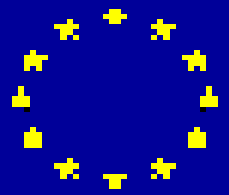
- Successful harmonization requires:
  - inclusiveness so that diverse viewpoints are considered
  - meaningful partnership between regulators & industry
  - commitment to long term goals

Summary Comments

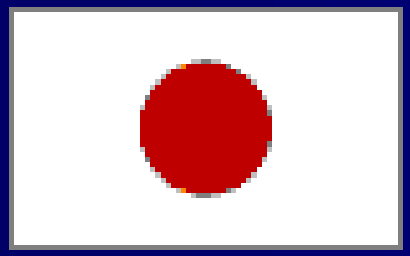
Thank you for your attention.







GHTF



Thank You …

Global Harmonization Task Force

Larry Kessler, Sc.D.
FDA, Chair GHTF
Janet Trunzo
AdvaMed, Vice Chair

Key Themes

- GHTF Background
- Program of work
- Emerging Asian harmonization
- Emerging device issues
- GHTF and the Future

Why GHTF?

- The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness / performance and quality of medical devices, promoting technological innovation and facilitating international trade.

More Why?

- Serves as an information exchange forum
- Countries with medical device regulatory systems under development can benefit from others' experience
- May pattern their practices upon those of GHTF founding members
- Avoid unnecessary (new) regulatory requirements

What: Organization

- Founded in 1992
- Steering Committee made up of equal number of industry and government regulators
- The chair rotates among the government regulators, held from January 2007-July 2008 by the US

What: Study Groups

Study groups are the engine of GHTF guidance development (over 30 posted)

- SG1: Premarket conformance
  - (Chair, Dr. Ginette Michaud, FDA)
- SG2: Postmarket vigilance/surveillance
  - (Chair: Jorge Garcia, TGA Australia)
- SG3: Quality Systems
  - (Chair: Egan Cobbold, Health Canada)
- SG4: Auditing
  - (Chair: Markus Zobrist, Swissmedic)
- SG5: Clinical effectiveness
  - (Chair: Dr. Susanne Ludgate, MHRA UK)

So What? Successes?!

- Adverse event reporting
- Health Canada maintains the electronic National Competent Authority Report (NCAR) system
- ISO 13485 and FDA Quality System Requirements
- Auditing strategies and format close
- Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)
- GHTF served as basis of Australian system!

Where are we headed?
Taking the Task Force Forward

- Guidance Implementation
- Organizational Logistics
- Expansion

Implementation

- Implement guidance documents
  - FDA making a concerted effort: working on 7 guidance documents
- Single audits used in multiple jurisdictions!
  - Canada-Australia and Canada-EU agreements
  - FDA-Canada Pilot Multipurpose Audit Program
  - FDA-EU discussions beginning on possible pilot
  - Encourage use of the AP (Accredited Persons)
- Improve operation of the National Competent Authority Report system

Organizational Logistics

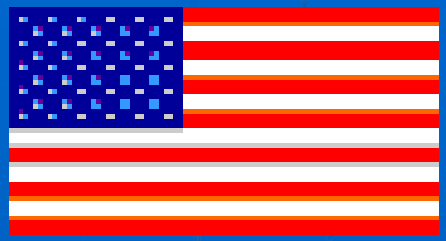
- Enhance web site utility and visibility
  - Attempt to create definitive regulatory source
  - Increased document availability: for example, *GHTF presentations on website*
  - Provide for links to translated documents
    - PAHO translated into Spanish and Portuguese
    - For example, can we documents in Mandarin?

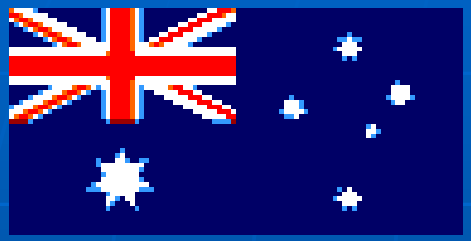
Expansion

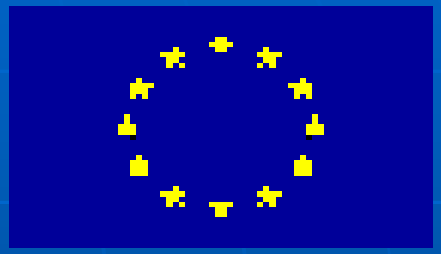
- Involve other countries, esp. AHWP, PAHO
- Work with ISO, IEC, others who share the GHTF mission
- GHTF Training Plan

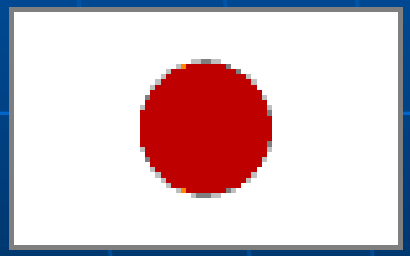
The Future is Now

- The GHTF has accomplished much
- Time to document those accomplishments
- Let's then build on this foundation and truly move toward the realization of global harmonization









Thank You …

Study Group 1

IVD Medical Devices – the GHTF Guidance Documents

Shelley Tang
Therapeutic Goods Administration
Australia

Petra Kaars-Wiele
EDMA Representative/
Abbott Laboratories
Germany

Overview of presentation

- IVDs as a sub-set of medical devices
- Essential Principles
- Classification
- Summary Technical Documentation (STED)
- Conformity Assessment

What is an IVD?

'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, 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 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,
- disinfection of medical devices,
- providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body,
- and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

What is an IVD?

- **IVD medical device:** A device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.
- Note: In some jurisdictions, some IVD medical devices may be covered by separate regulations.

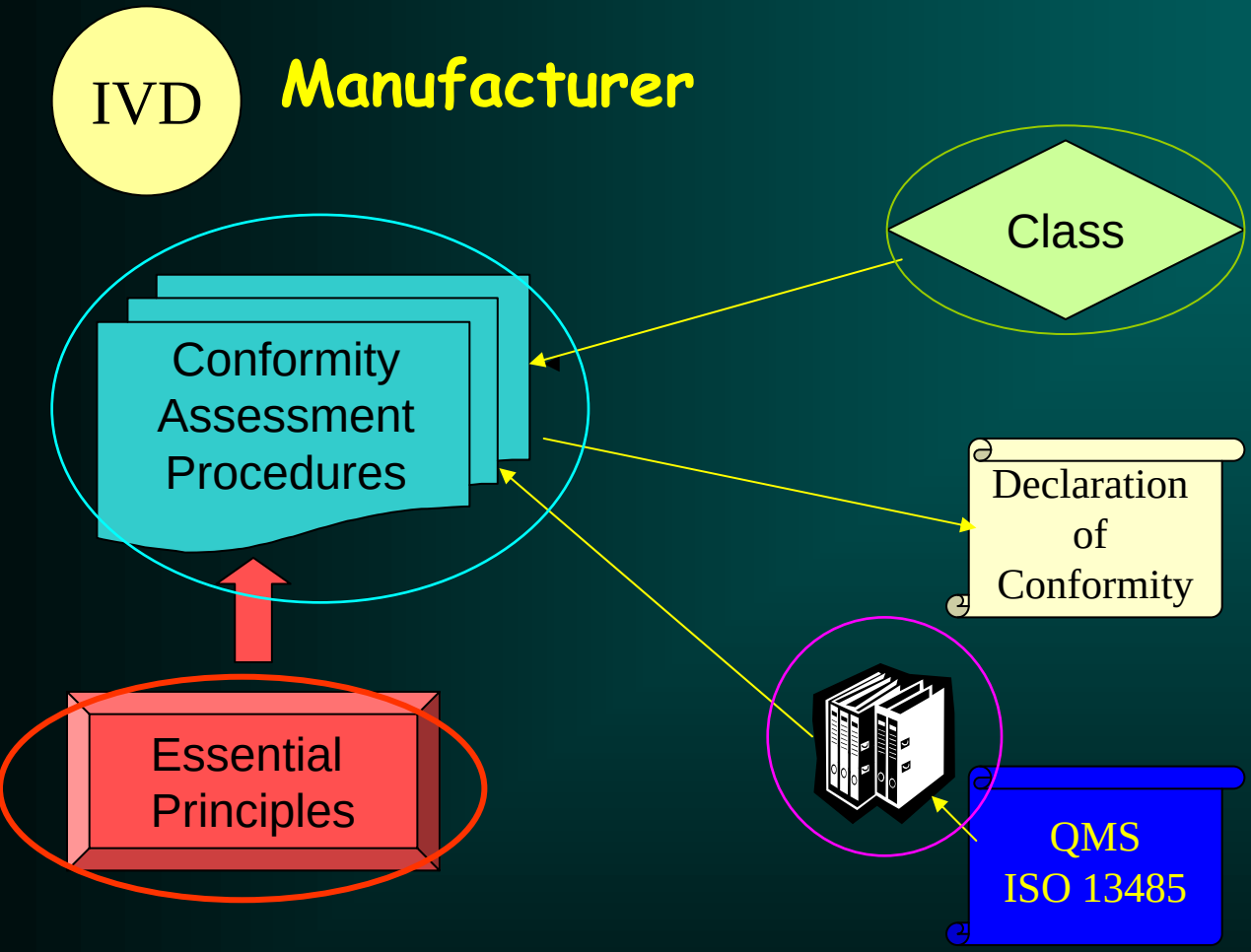
GHTF documents on IVDs - General

- SG1/N012 *Role of Standards in the Assessment of Medical Devices.*
- SG1/N029 *Information Document Concerning the Definition of the Term 'Medical Device'.*
- SG1/N041 *Essential Principles of Safety and Performance of Medical Devices.*
- SG1/N043 *Labelling for Medical Devices.*

GHTF documents on IVDs - Specific

- SG1(PD)/N045R13 *Principles of In Vitro Diagnostic (IVD) medical devices Classification*
- SG1(PD)/N046R4 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) medical devices*
- SG1(PD)/N063 (early Draft) *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices (STED)*

The Roadmap



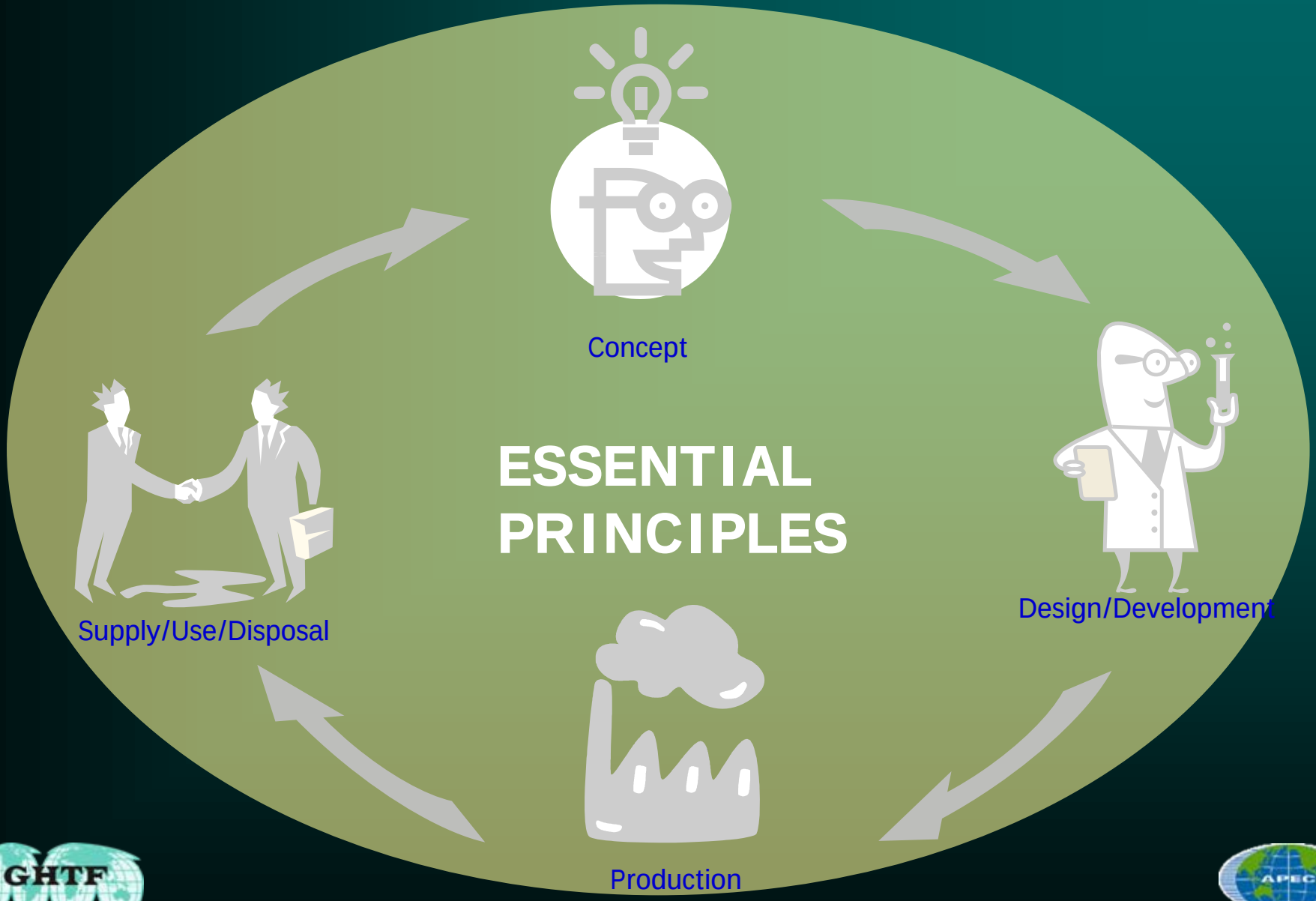
Post-Market Respons-ibilities

Essential Principles

Essential Principles

- All IVDs must meet the Essential Principles for quality, safety and performance
- EPs underpin the regulatory framework
- Compliance with EPs may be demonstrated by use of standards – see GHTF SG1-N012R10 *Role of Standards in the Assessment of Medical Devices*

Essential Principles



Essential Principles

- EPs cover design, manufacture, clinical performance, and overall safety to user and person being tested
- EPs define risks to be managed/ results to be achieved, but do not specify how
- Manufacturers determine which EPs are applicable
- Compliance with EPs is the manufacturer's responsibility

Essential Principles

- GHTF document on Essential Principles includes IVDs in its scope.
- Six general EPs – apply to all medical devices, including IVDs
- 11 specific EPs, which may or may not apply to a particular device, depending upon its type and construction

General Essential Principles

- Must not compromise health and safety
- Conforms to safety principles, taking into account the general state-of-the-art
- Suitable for intended purpose
- Performs as intended during determined shelf life under normal conditions of use
- Performs as intended when subjected to prescribed conditions of transport and storage
- Benefits outweigh risk

Specific Essential Principles

Devices with a diagnostic or measuring function (5.10)

- Sensitivity, specificity, trueness, repeatability, reproducibility, control of interference, and limits of detection
- Traceability of controls and calibrators

Self-Testing (5.15)

- Consider the user of the test - easy to use instructions/protocol
- Reduce risk of error in use and interpretation
- Design allows for verification by user

Specific Essential Principles (cont)

- Performance evaluation (5.17) – “all data generated in support of performance evaluation should be obtained in accordance with the relevant requirements applicable in each jurisdiction”...
- Just what is required in relation to clinical evidence for IVDs not yet determined in GHTF guidance.

Classification

Classification

- The GHTF framework proposes a risk based classification system for all IVDs

- The determination of classification will be based on a set of rules derived from those features that create the risk associated with an IVD

Why classify?

Class determines level of regulatory oversight

- Class determines the relevant conformity assessment procedures
- The class is determined by applying a set of rules
- Rules based classification allows greater flexibility
  - New diseases, emerging technologies
- Classification is the responsibility of the manufacturer

How to determine class?

Responsibility of the manufacturer

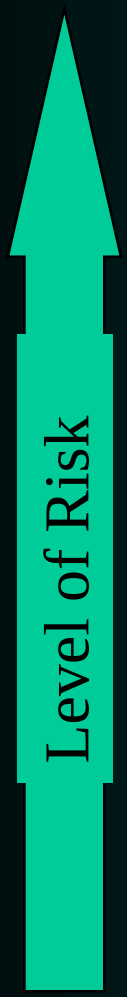
- Decide if the product is an IVD, based on intended use and using the definition
- Consider the Rules. An IVD with multiple intended purposes will be placed in the highest applicable class
- Determine that special national rules do not apply
- Where more than one Rule applies, the Rule which places the IVD in the highest class applies

Classification

Risk Factors

- The intended use and indications for use
  - Specific disorder, population, condition or risk factor for which the test is intended
- The technical/scientific/medical expertise of the intended user
- The importance of the information to the diagnosis
  - Sole determinant or one of several
- The impact of the result (true or false)

Risk Classes



Class D IVD - High Individual Risk and High Public Health Risk

E.G. HIV blood donor screening, HIV blood diagnostic

Class C IVD – High Individual and/or Moderate Public Health Risk

E.G. Blood glucose self-testing, HLA typing, PSA screening, Rubella

Class B IVD – Moderate Individual and/or Low Public Health Risk

E.G. Vitamin B12, pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips

Class A IVD – Low Personal/No Public Health Risk

E.G. Clinical Chemistry Analyser, prepared selective culture media

Class D IVD

High Public Health Risk
and/or
High Individual Risk

Includes IVDs that are used for

- screening of the blood supply and organ and tissue donations for pathogens , eg IVDs used for screening for infection with HIV, HCV, HBV, HTLV
- Detecting the presence of a transmissible agent likely to cause a life-threatening illness with a threat to public health – example as above
- Blood grouping or tissue typing to ensure compatibility where there is an individual high risk, eg ABO, rhesus, Kell, Kidd and Duffy

Class C IVD

High Individual Risk and/or Moderate Public Health Risk

Includes IVDs that are used for

- Blood grouping, tissue typing, not in Class D
- Detection of transmissible agents
  - Sexually transmitted
  - In CSF or blood (limited risk of propagation)
  - Likely to cause death or severe disability
- Immune status in pregnancy
- Human genetic testing
- Detection of congenital diseases in the foetus

Class C IVD (cont...)

High Individual Risk and/or Moderate Public Health Risk

Includes IVDs that are used for

- Infective disease status in high individual risk situations
- Screening for selective therapy and management, for disease staging, or diagnosis of cancer
- Monitor levels of medicines etc, in high-risk patient management situations (cardiac markers, prothrombin time testing)
- Management of patients with life-threatening infectious disease (HCV/HIV viral load, genotyping or subtyping)
- Self-testing, in determining a medically critical status.

Class B IVD

Moderate Individual Risk and/or Low Public Health Risk

Includes IVDs that

- are used for self-testing, where results are not medically critical or require confirmation (pregnancy testing, fertility testing, urine test strips)
- Are not covered by other Rules (blood gases, hormones, vitamins, enzymes, metabolic markers)
- Are intended to be used as controls without a quantitative or qualitative assigned value (do not validate the decision on the release of patient results)

Class A IVD

Low Individual Risk and/or Low Public Health Risk

Includes IVDs that are

- Reagents or other articles used in in vitro diagnostic procedures (selective/differential microbiological media, identification kits for cultured micro-organisms, wash solutions)
- Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures
- Specimen receptacles

STED-
Summary Technical Documentation

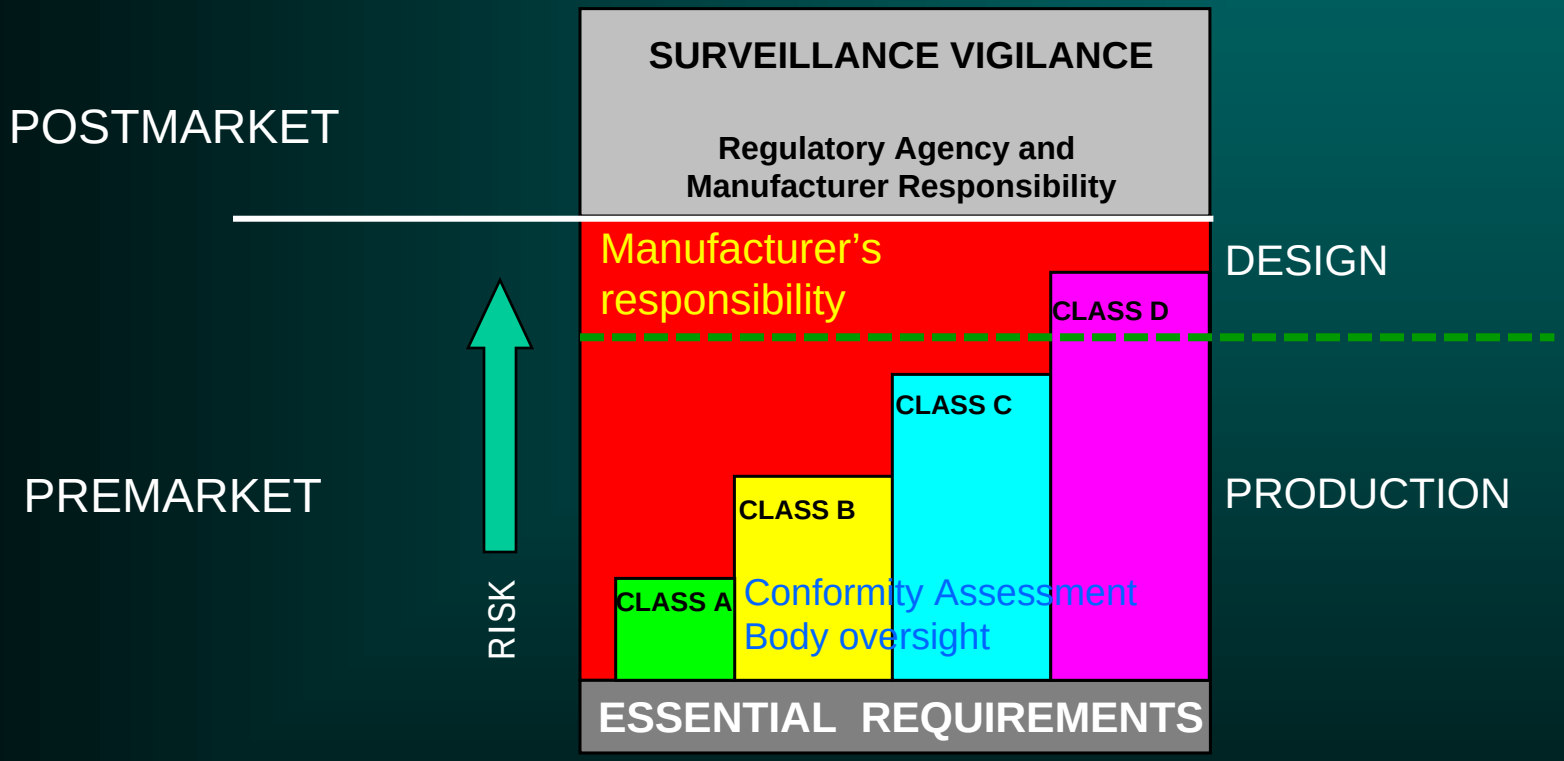
Content of STED

- Preface:
  - The STED does not represent the full technical documentation which is controlled under the Quality System
  - STED should be in a language acceptable to the reviewing organization
  - Depth and detail may be dependant on classification and risk, whether it is novel technology or already marketed

Content of STED

- General description and list of specified features
- Set of labels and list of language variants
- Summary of technical documentation concerning design and manufacturing
- Essential Requirement Checklist
- Summary of risk analysis and mode of control
- Summary of verification and validation studies – Performance Evaluation

Conformity Assessment


SURVEILLANCE VIGILANCE
Regulatory Agency and Manufacturer Responsibility
POSTMARKET
Manufacturer's responsibility
DESIGN
CLASS D
CLASS C
PREMARKET
CLASS B
PRODUCTION
RISK
CLASS A
Conformity Assessment Body oversight
ESSENTIAL REQUIREMENTS

Conformity Assessment - Elements

- Quality Management System
- Documentation (STED= Summary Technical Documentation)
- Declaration of Conformity
- Registration of Manufacturer and their Products
- Systematic Post-Market Surveillance System

Type of Quality System

- ISO 13485 — Certified full Quality System with design Control
- ISO 13485 — Certified full Quality system **except** design control (alternative for Class A and B products only)

- In assessing the Quality Management System for Class B to D IVDs, the Regulatory Authority or Conformity Assessment Body will take into account relevant existing certification and conduct on-site audit only with reasoned justification.

STED = Summary Technical Documentation

- Technical documentation is to be prepared for all IVDs according SG1(PD)/N063 (early draft)
- Submission and review by the authorities not required for Class A and B, but if in justified cases may be submitted on request.
- Review by the authorities for Class C and D, based on risk of the products and experience of the manufacturer

Declaration of Conformity

- A declaration made by the manufacturer
- Name and address of the responsible manufacturer
- Identification of the device (product name, product number, GMDN code)
- Statement that the device complies with
  - The Essential Principles of Safety and Performance
  - The Classification and Conformity Assessment Procedure
  - List standards used in the Conformity Assessment Procedure
- Dated and signed by the manufacturer (appropriate senior personnel)

Registration of Manufacturer and Their IVD Products

- At minimum the Regulatory Authority maintains a registrar of products marketed in their country (manufacturer and product listing, and maybe importers)

Systematic Post-Market Surveillance

- Manufacturer holds a complaint handling systems and initiates appropriate investigations
- Manufacturer captures information learnt from the market and the users and takes actions if required
- Manufacturer reports any potential medical events to the authority, where the event occurred
- Regulatory Authority may request information or audit the manufacturer in justified cases

Quality System or Surveillance Audits

- It is not passing an exam!!!!
- Demonstration of continual operation and compliance
- Supports continuous improvement of products and processes

Conformity Assessment

- Considerations for Regulatory Authorities
  - Public health protection priorities (risked based, not every product has the same risk)
  - Proportionality of methods to public health benefits
  - Access to market to ensure efficient diagnosis of patients and state-of-the-art products
  - Relevant existing certification
  - Resources
    - Funding
    - Expertise
    - Efficient use
    - Timeliness (eg - impact on market viability)

In Practice

- Class D
  - The manufacturer has a full Quality System certificate which includes design control according ISO 14835
  - Submission of the STED and Declaration of Conformity
  - Pre-Market Review by the Regulatory Authority or the Conformity Assessment Body (3rd party) of documentation and performance of the product to ensure that the Essential Principles are fulfilled and the claims of the products are met
  - Review Adverse Event Reporting process and procedure
  - Open questions to be discussed with the manufacturer and/ or representative
  - Add product to registrar

In Practice

- Class C
  - The manufacturer has a full Quality System certificate which includes design control according ISO 14835
  - Submission of the STED and Declaration of Conformity
  - Review by the Regulatory Authority or the Conformity Assessment Body (3rd party) of documentation and performance of the product to ensure that the Essential Principles are fulfilled and the claims of the products are met (maybe done during a pre-market audit on-site)
  - Review Adverse Event Reporting process and procedure
  - Open questions to be discussed with the manufacturer and/ or representative
  - Add product to registrar

In Practice

- Class B
  - The manufacturer has a Quality System certificate according ISO 14835, which need not include design control
  - Preparation of STED and maintained by the manufacturer, pre-market submission is not required, but in justified cases may be reviewed
  - Declaration of Conformity is prepared by the manufacturer and submitted to the Regulatory Authority
  - Verify that Declaration of Conformity is appropriate
  - Ensure Adverse Event Reporting process and procedure is in place
  - Add product to registrar

In Practice

- Class A
  - The manufacturer has a Quality System certificate according ISO 14835, which need not include design control
  - Preparation of STED and maintained by the manufacturer, pre-market submission is not required, may be reviewed during surveillance audits or if there are regulatory concerns
  - Declaration of Conformity is prepared by the manufacturer, not submitted to Regulatory Authorities
  - Ensure Adverse Event Reporting process and procedure is in place
  - Add product to registrar

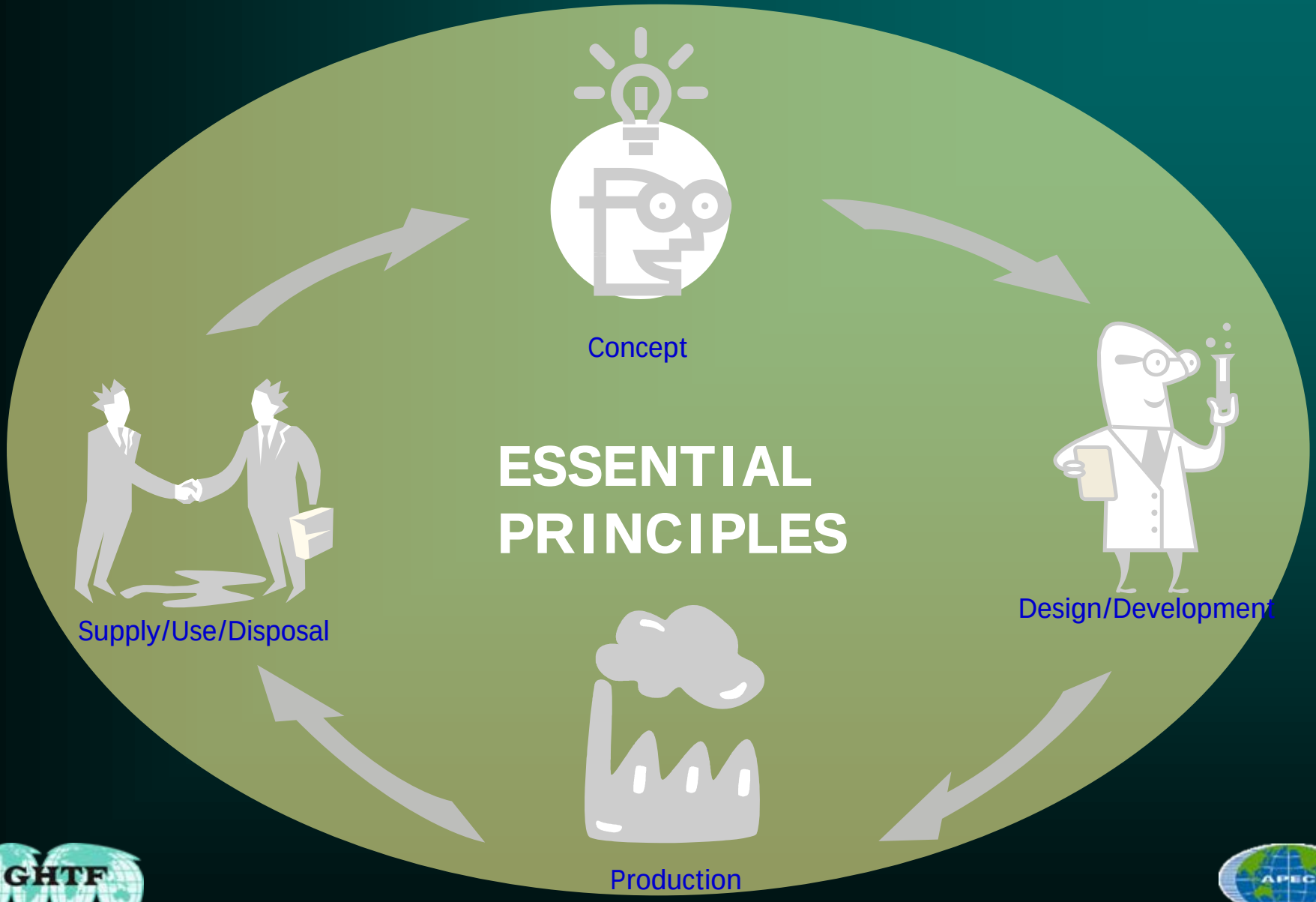
Any Questions?

Medical Devices – Integrity in the Supply Chain

Roles and Responsibilities

Shelley Tang
Therapeutic Goods Administration
Australia

Whole of Life Cycle Approach



Manufacturer's responsibility

- In most Founding Member jurisdictions manufacturer takes ultimate responsibility for
  - Initial design
  - Compliance with Essential Principles/Safety and effectiveness requirements
  - Production
  - Ongoing monitoring of performance in the marketplace
    - Response to adverse events
    - Reporting of corrections or removal for safety reasons

Where device is imported...

- Regulatory authority in importing country needs a responsible body over which they have jurisdiction
- Manufacturer (in general) needs person(s) “on the ground” to enable manufacturer to meet obligations
- Known as importer, sponsor, initial distributor, Authorised Representative, Official Correspondent

Importer's responsibility

- Authorised by the manufacturer
- Takes legal responsibility for supply in the importing jurisdiction
- Interacts with Regulatory Authority on behalf of manufacturer
- Feeds back information on performance of the device to the manufacturer
- Keeps records of distribution

Australia

- Sponsor
  - Must hold information or have written agreement with manufacturer...
  - “includes” the device on the ARTG
  - Takes responsibility for recall and reporting
    - Annual reports
    - Serious adverse events (time frames mandated)
    - Non-compliance with regulatory requirements
  - Complies with conditions imposed on supply
  - Must give information to the TGA as required
  - TGA may inspect premises and take samples

Canada

- Importers and distributors require
  - an establishment licence
  - Documented procedures for distribution records, complaint handling and recalls
  - For Class II, III or IV devices, documented procedures for handling, storage, delivery, installation, corrective action and servicing
- Manufacturer and importer must each report serious adverse events (mandatory time-frames)
- Implant registration cards held by manufacturer

Europe

- Manufacturer works through Notified Body
- Manufacturer must have **a** designated responsible person established in the Community
- AR or importer must be identified on the label
- AR can act on behalf of a manufacturer
  - Can affix CE mark
  - Can prepare and sign DoC
- Manufacturer or designated responsible person must inform CA of address and category of devices supplied

Europe (new requirements)

From 2012

- Data to be stored in the European Databank
  - Registration of manufacturers
  - Certificates (issued, modified, supplemented, suspended, withdrawn or refused)
  - Data obtained in accordance with vigilance procedures
  - Registration of authorised representatives
  - Data on clinical investigations

Japan

- Manufacturer responsible for production only
- Market Authorisation Holder (MAH) responsible for
  - Quality and safety standards
  - Good Quality Practice
    - Shipping and receiving
    - Notifying MHLW of manufacturing changes
    - Release criteria
    - Recalls
  - Good Vigilance Practice
    - Safety of products after release into the marketplace

USA

- Foreign manufacturers must designate a US agent
- Initial importer must
  - Register establishment
  - Report serious adverse events to FDA
  - Report MDRs to manufacturer
  - Report to FDA on corrections and removals
  - Implement tracking procedures for specified devices

USA (cont)

- Distributor must keep records of complaints and make records available to the FDA
- Dealers and distributors in some cases (eg electronic products for which performance standards exist) must hold such information as is necessary to identify and locate first purchasers

Issues

- All jurisdictions know who is responsible for supply of the device
- Not all jurisdictions require address of responsible person on the label
- Most have mandatory reporting requirements
- Links between importer and manufacturer vary in strength
- Tracking requirements vary

Any Questions?

THE ROLES & RESPONSIBILITIES IN THE SUPPLY CHAIN FOR MEDICAL DEVICES: Safety, Performance and Conformity Assessment Throughout the Total Product Life Cycle

Datuk Dr M S Pillay, AHWP

APEC Asia-Pacific Economic Cooperation

GHTF

AHWP

INTRODUCTION

- Assuring medical device safety requires oversight of the use of medical devices
- All elements of control from design through disposal are required to be put in place to ensure continued safety and performance throughout total life cycle
- Different parties are involved

TOTAL PRODUCT LIFE CYCLE

Manufacturing, import, packaging, labelling, storage, tracking, surveillance/vigilance

Advertising, distribution, transportation, storage, tracking

Installation, usage, maintenance, surveillance/vigilance, incident reporting

PRE-MARKET

PLACEMENT ON-MARKET

POST-MARKET

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ROLES & RESPONSIBILITIES OF MANUFACTURER/AUTHORIZED REPRESENTATIVE

- Ultimate regulatory responsibility
- To ensure safety and performance of medical devices are maintained throughout total life cycle of the device
- Well addressed in many GHTF documents
- Issues: Training of users and 3rd Party Service Providers

ROLES & RESPONSIBILITIES OF DISTRIBUTOR/RETAILER

- To ensure safety, quality and performance of medical devices are maintained throughout the distribution chain
- This includes storage, transportation, distribution, installation

ROLES & RESPONSIBILITIES OF DISTRIBUTOR/RETAILER

- Issues:
  - Storage, transportation & tracking of device
  - Communication channel with manufacturer/retailer/user
  - Good Distribution Practise
  - Quality of service
  - Regulatory control, standards, guidelines

ROLES & RESPONSIBILITIES OF USER

- To ensure medical devices are used in accordance to the intended use in accordance with the specifications
- To ensure continued safety and performance of medical devices from the point of installation through to disposal
- To ensure the device is decommissioned and disposed accordingly

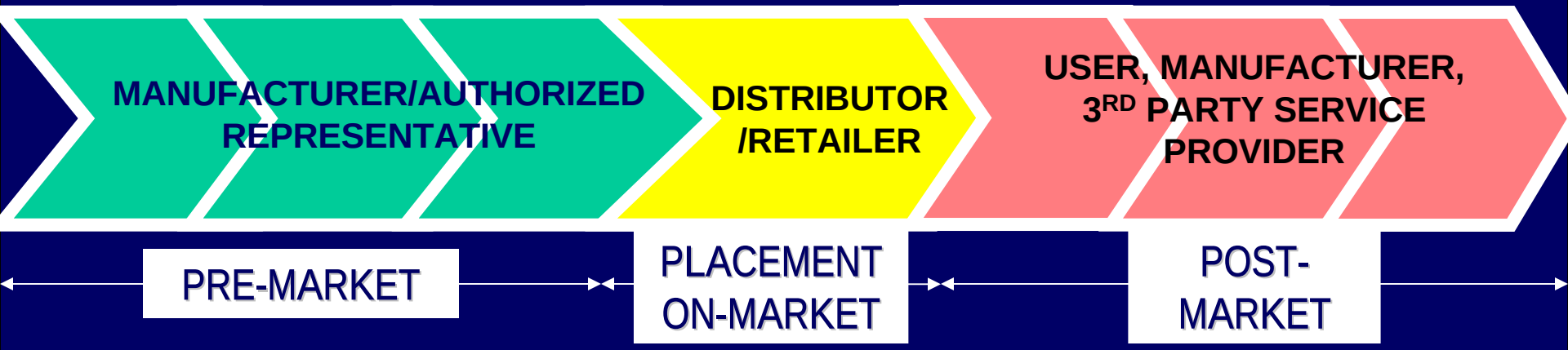
ROLES & RESPONSIBILITIES OF USER

- Issues:
  - Usage of device, no misuse
  - Installation, testing & commissioning
  - Maintenance by 3rd Party service provider
  - Safety of patients, users & public
  - Competency of user & maintenance staff
  - Performance monitoring
  - Adverse event reporting
  - Device Tracking
  - Disposal
  - Regulatory control, standards, guidelines

Manufacturing, import, packaging, labelling, storage, tracking, surveillance/vigilance

Advertising, distribution, transportation, storage, tracking

Installation, usage, maintenance, surveillance/ vigilance, disposal, incident reporting



TO ENSURE SAFETY AND PERFORMANCE OF MD THROUGHOUT TOTAL LIFE CYCLE:

Do we need to include retailer, user and 3rd party service provider and their respective activities into the scope of MD regulation??

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Implementation of the GHTF Model for Device Regulation

The Australian Experience

Shelley Tang
Therapeutic Goods Administration
Australia

The Framework

- Essential Principles
- Classification Rules
- Conformity Assessment Procedures
- Use of standards

Implementation

- Conformity assessment by the TGA required for
  - Australian manufacturers
  - Devices of animal/microbial/recombinant origin
  - Devices incorporating a medicine
- CE certification generally accepted for other devices
  - Application audit for Class III and AIMD
- Must have DoC to Australian requirements

Preferred Model

- Implementation through MoUs, MRAs
- Ensures assessment to Australian requirements
- Minimises regulatory burden
- Facilitated by adoption of GHTF model

Issues

- Adoption of standards
  - Mapping against EPs
  - Mandatory vs non-mandatory
  - Updating issues
- Differences in classification (between jurisdictions)
  - Actual differences
  - Differences in interpretation
  - Borderline products
- Differences in definitions
- Third party issues

Thank you

TGA

Overview of Global Harmonization Task Force Study Group 5

Greg LeBlanc and Johan Brinch
GHTF SG5

Slide Development with assistance of Herb Lerner

Background

- SG5 was established at the June 2004 meeting of the GHTF Steering Committee
- First meeting was January 2005
- Mandate: to work towards convergence of clinical evidence requirements which should yield common data for the purpose of mutual acceptance by global regulators

“Assignments”

- First phase:
  - harmonise clinical definitions;
  - review existing GHTF documents and applicable ISO/ICH documents, to assure terminology is consistent and interfaces are clear;
  - Develop guidance on how to conduct and document the clinical evaluation; and
  - harmonise the content and format for clinical evaluation reports.
- Second phase:
  - harmonise principles to determine when clinical investigation, as opposed to other forms of clinical evidence, is necessary

“Assignments”

- Current work
  - harmonise principles to determine when post-market clinical follow-up studies are required, and the content of such a study
  - evaluate the need for harmonization of adverse event reporting (future proposal)

Current Status

- So far, we have held 12 meetings
- Meetings occur approximately once every 4 months
  - Most recent: Brussels, Belgium, January, 2008
  - Next: Tokyo, Japan, May 2008

Current Status

- So far, we have produced:
  - Two “final” documents:
    - *Clinical Evidence – Key Definitions and Concepts* (GHTF SG5/N1:2007)
    - *Clinical Evaluation (GHTF SG5/N2:2007)*
  - *Two “In Progress” documents*
    - *Clinical Investigation- GHTF SG5/N3 (est:2008)*
    - *Post-market Clinical Follow-up SG5/N4 (est:2008/Q1 2009)*
    - *Plus adaptation of N2 document for IVDs*
  - Memorandum of Understanding with ISO TC 194 (responsible for ISO 14155) – close liaison necessary to avoid overlap

Definitions and Concepts Document

- Focuses on key definitions related to clinical investigations and the clinical evaluation process only
- Defines:
  - Clinical Investigation
  - Clinical Evaluation
  - Clinical Data
  - Clinical Evidence

Definitions

- Clinical Investigation
  - "Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device"

Definitions

- Clinical Data
  - "Safety and/or performance information that are generated from the clinical use of a medical device"

Definitions

- Clinical Evaluation
  - "The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer."

Definitions

- Clinical Evidence
  - "The clinical data and the clinical evaluation report pertaining to a medical device."

Clinical Evaluation – What Is It?

- Process for assessing the clinical information known about a device to determine whether the relevant Essential Principles for safety and performance have been satisfied
  - Relevant Clinical Information Includes:
    - Scientific Literature
    - Clinical Experience
      - e.g. market experience, adverse event reports
    - Clinical Investigations

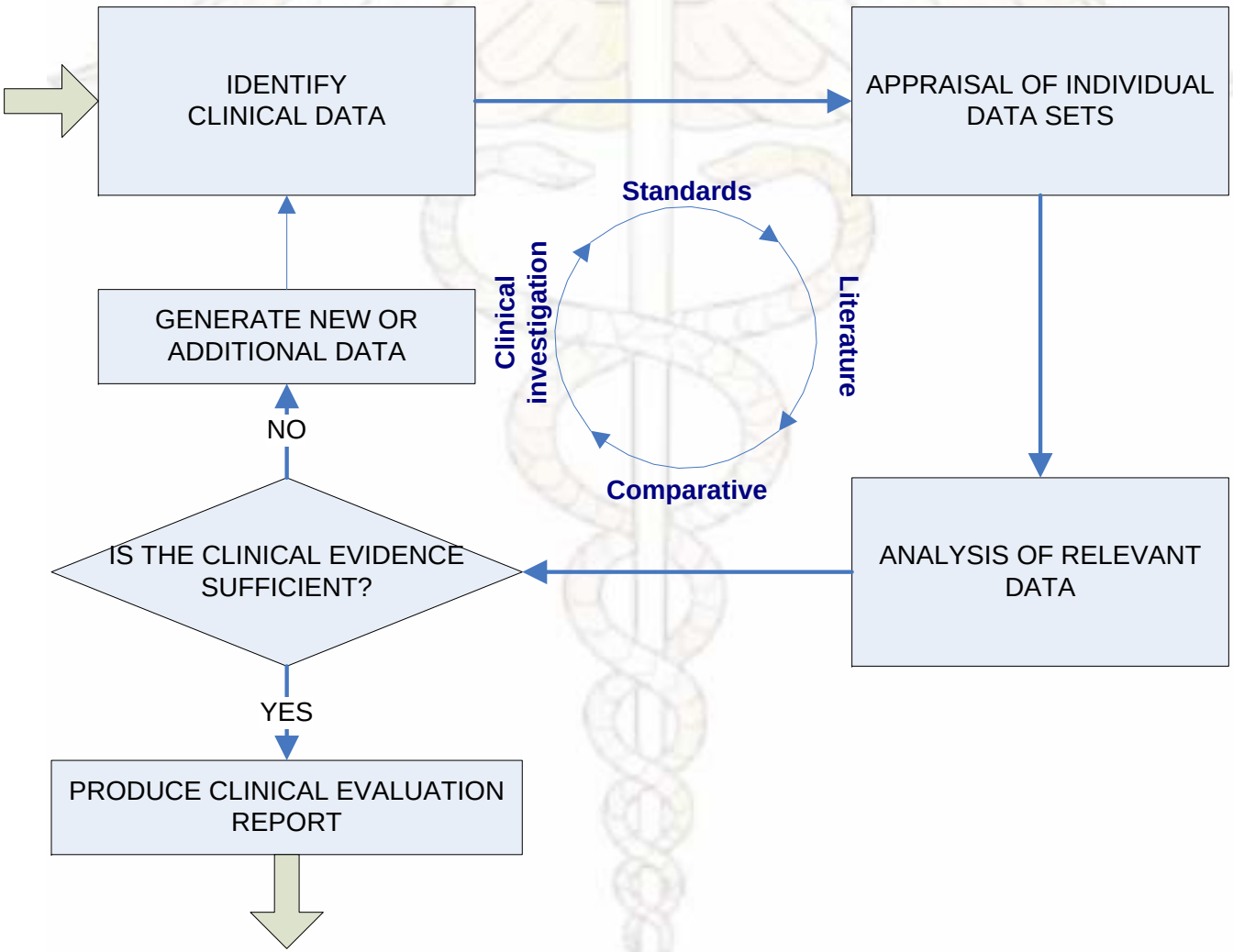
Clinical Evaluation – What Is It?

- a critical appraisal of available clinical information
- to determine if a favorable benefit-to-risk ratio exists for the device
- nature and amount of information needed will vary with the type of device, conditions of use, and experience with similar devices, along with other available data (e.g. preclinical/bench-top)

Clinical Evaluation – What Is It?

- Each device assessed individually, but builds off of knowledge obtained from similar devices
- Context of Risk Assessment and Analysis is critical
- Ongoing process as new information emerges (e.g. post-market)

STED & clinical evidence



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Then What?

- Contents of Clinical Evaluation Report and Clinical Data constitute Clinical Evidence
- Used as part of technical documentation (may be submitted for review as part of STED) to support market authorization

Contents of Clinical Evaluation Guidance

- Sources of information
- How to conduct and document literature reviews
- How to incorporate various information sources
- How to report the clinical evaluation

Clinical Evaluation – General Principles

- What is the scope of a Clinical Evaluation?
  - Comprehensive analysis of available pre- and post-market clinical data
  - May be specific to device in question or related devices
  - Should address clinical claims and all labeling, particularly warnings/precautions

Clinical Evaluation – General Principles

- What is the scope of a Clinical Evaluation?
  - Should be defined prior to undertaking, based on relevant Essential Principles that need consideration from a clinical perspective
  - Considerations include:
    - Are there any design features or target populations that require specific attention?
    - Can data from comparable devices be used?
    - What data source(s) and type(s) can be used?

Clinical Evaluation – General Principles

- Who should perform it?
  - Someone with “suitable qualifications”
  - Must be justifiable choice
  - Should possess knowledge of:
    - Device technology and application
    - Research methodology
    - Diagnosis and management of target conditions

Clinical Evaluation – General Principles

- How is it performed?
  - Three discrete stages:
    - Identification of pertinent data (may include citation of pertinent standards where appropriate)
    - Appraisal of each individual dataset in terms of relevance, quality, applicability, etc.
    - Analysis of individual data sets with conclusions drawn for the subject device
  - As outlined on previous slide with figure

Clinical Evaluation – Sources of Data

- Literature searching
  - For subject device or comparable devices
  - Should follow a predefined protocol and have a final report
- Clinical experience
  - e.g. surveillance reports, adverse event databases, compassionate use
  - Requires some caution re: useability
- Clinical Investigations

Clinical Evaluation – Appraisal of Data

- Each piece of data needs to be objectively reviewed for quality and relevance
  - Then need further appraisal as to the contribution to establishing safety and performance

Clinical Evaluation – Analysis of Data

- Do appraised data sets collectively demonstrate clinical performance and safety of device in question?
- Relative weighting of datasets must be factored in, but all datasets should be included in analysis
- How do combined data demonstrate/fail to demonstrate safety and performance?

Clinical Evaluation – Report

- A Clinical Evaluation Report should be prepared to outline the process and conclusions
- Should be sufficient to be read as a stand-alone document by an independent third party
- Should be signed and dated by the evaluator(s) and accompanied by justification of choice of evaluator(s)

Clinical Evaluation Guidance – Appendices

- Include:
  - Suggested Literature Search Report format
  - Possible methodology for literature screening
  - Sample criteria for data appraisal
  - A sample method of appraisal
  - Suggested Clinical Evaluation Report format

Clinical Investigations Document

- Put forward to Steering Committee at this meeting for advancement as Proposed Draft

Clinical Investigations Document

- Provides guidance on use of Clinical Investigations as a tool for gathering Clinical Data not available through other means
- Provides general direction on standards for conducting study, basic principles of study design, etc.

Clinical Investigations Document

- Introduction and Scope Statements
  - Points to ISO 14155 as standard for the conduct of a Clinical Investigation and the contents of a Clinical Investigation Plan
  - Indicates that guidance was drafted primarily with use in pre-market applications in mind, but that some concepts will be broadly applicable to post-market clinical follow-up studies as well

Clinical Investigations – General Principles

- When do you undertake one?
  - When necessary to provide the clinical data not available through other sources (e.g. preclinical or literature) required to demonstrate conformity to Essential Principles
    - Can be clarified by:
      - Reviewing relevant Essential Principles,
      - Performing risk management activities
      - Conducting a clinical evaluation

Clinical Investigations – General Principles

- How does risk analysis factor in?
  - Helps determine what clinical evidence may be required for a particular device
  - Where risk analysis and clinical evaluation indicate that there are residual risks that cannot be adequately addressed through other means
  - See ISO 14971

Clinical Investigations – General Principles

- When is it justified?
  - Should avoid unnecessary experimentation on human subjects
  - Therefore, only perform a clinical investigation when:
    - It is necessary (as outlined above)
    - It is properly designed
    - It is ethical
    - Proper risk management procedures are followed
    - Compliant with all legal and regulatory requirements

Clinical Investigations – Principles of Design

- Design should aim to ensure that necessary clinical data are obtained
- Many factors may influence extent of data requirements
- As a general rule, devices based on new technologies or extending an intended use beyond current experience are more likely to require data derived from a Clinical Investigation

Clinical Investigations – Principles of Design

- Examples of specific considerations for device study designs:
  - Clear statement of objectives
  - Appropriate study populations
  - Minimization of bias
  - Identification of confounding factors
  - Appropriate controls where necessary
  - Design configuration
  - Type of comparison (e.g. non-inferiority)

Clinical Investigations – Principles of Design

- Design should maximize clinical relevance of data while minimizing confounding factors
  - Randomized, controlled, double-blind studies are historical “gold standard” but this design can seldom be appropriately applied to a device trial

Clinical Investigations – Principles of Design

- Statistical considerations very important
- Statistical plan must be prospectively defined and based on sound scientific principles and methodology
- Design should ensure that statistical evaluation reflects a meaningful and clinically significant outcome

Clinical Investigations – Principles of Design

- Conduct of the study:
  - A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of subjects, the integrity of the data, and it suitability for demonstrating conformity to the relevant Essential Principles
  - ISO 14155 outlines Good Clinical Practice for medical device investigations

Clinical Investigations – Principles of Design

- Outcome of an investigation should be documented in a final Study Report
  - This report forms part of the clinical data that is included in the clinical evaluation process

Clinical Investigations – Ethical Considerations

- Should follow Declaration of Helsinki
- Should be used only when data cannot be obtained through other methods
- Design and endpoints should be adequate to address residual risks
- Should follow a scientific and ethical investigational process not exposing subjects to undue risks or discomfort
- Undergo ethics review and regulatory oversight in conformity to local requirements

Impact of SG5 Documents

- N1 document provides a set of definitions that can be universally applied to the discussion of clinical evidence
  - Consistent terminology for everyone involved

Impact of SG5 Documents

- N2 document provides guidance surrounding the concept of clinical evaluation
  - What information should be satisfactory to support a device's presence in the marketplace
  - Outlines the elements to include in the process & what does and does not constitute clinical data

Impact of SG5 Documents

- N2 document provides guidance surrounding the concept of clinical evaluation
  - How the clinical evaluation report forms part of the clinical evidence
  - If the document is followed, the format and content of the resultant report should be considered acceptable by reviewers

Impact of SG5 Documents

- N3 document provides guidance surrounding the design and conduct of clinical investigations
  - When a study is required/justified
  - Appropriate design and conduct
  - How the results are integrated into clinical evaluation process

Current Work Items for SG5

- Adapt Clinical Evaluation document to address IVDs
  - What does “Clinical Evaluation” really mean for IVDs?
  - Being undertaken with co-operation of IVD Subgroup of SG1

Current Work Items for SG5

- Clinical Investigation document
  - Publication as draft for public comment

Current Work Items for SG5

- Post-Market Clinical Follow-Up Document
  - When should Post-Market Clinical Follow-Up Studies be considered?
  - How do they fit in to the “big picture”?
  - Document will be out for public comment soon

Going Forward

- Continued liaison with ISO TC 194 to examine areas of common interest
- Proposed New Work Item regarding Clinical Investigation Adverse Event reporting
- Assess whether there other new topics should be addressed

THANKS!

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Overview of GHTF SG2 and NCAR

Dr Jorge Garcia –Therapeutic Goods Administration- Chairman GHTF SG2
Dr Philippe Auclair - Abbott Vascular– EUCOMED

Overview of this presentation

- what is post-market surveillance?
- membership…
- what we've done so far…
  - adverse event reporting
  - other postmarket surveillance
  - NCAR
- what we plan to do in the future…

Membership…

Regulatory Agencies

USA/Canada

- **Brady**, Mary, [FDA]
- **Segstro**, Mark,[Health Canada]

Europe

- **Demade**, Isabelle, [EC]
- **Antunes**, Miguel, [INFARMED]
- **Stösslein**, Ekkehard, [BfArM]

Japan/Australia

- **Eno**, Hideo, [MHLW]
- **Ishii**, Kensuke, [PMDA]
- **Garcia**, Jorge, [TGA]

Industry Associations

USA/Canada

- **Khosravi**, Ben, [AdvaMed]
- **Kroger**, Larry, [MITA/NEMA]
- **Stitz**, Klaus, [MEDEC]

Europe

- **Auclair**, Philippe, [EUCOMED]
- **Wallroth**, Carl, [EUROM VI]

Japan Australia

- **Ishikawa**, Hiroshi, [JFMDA]
- **Arima**, Takehiko, [JFMDA]
-

Post-market Surveillance

- “The pro-active collection of information on quality, safety or performance of Medical Devices after they have been placed in the market” – Reference : GHTF SG2 N47R4
- A balanced Post-Market Surveillance system will contain an appropriate mix of proactive and reactive activities.

Post-market Vigilance (Adverse Event Reporting)

- (Broadly speaking) Vigilance is the reporting and investigation of adverse events and incidents. Both the manufacturer and the Regulatory Authority play major roles.
- SG2 now prefers to use the term “Adverse Event Reporting”

Post-market Surveillance

Post-Market Surveillance Information is used for:

- Injury prevention
- Development of standards
- Regulatory refinement
- Product improvement

What we've done so far…

Adverse Event Reporting (AER)

SG2 Guidance
Adverse Event Reporting by Manufacturers

- SG2-N21R8: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative
- SG2/N31R8: Proposal for Reporting of Use Errors with Medical Devices by their Manufacturer or Authorized Representative
- SG2/N32R5: Universal Data Set for Manufacturer Adverse Event Reports
- SG2-N36R7: Manufacturer's Trend Reporting of Adverse
- SG2-N33R11: Timing of Adverse Event Reports
- SG2-N68R3: Who Should Adverse Event Reports be Sent To?

GHTF SG2 N54R8

SG2 Guidance

Report Handling & NCAR Program

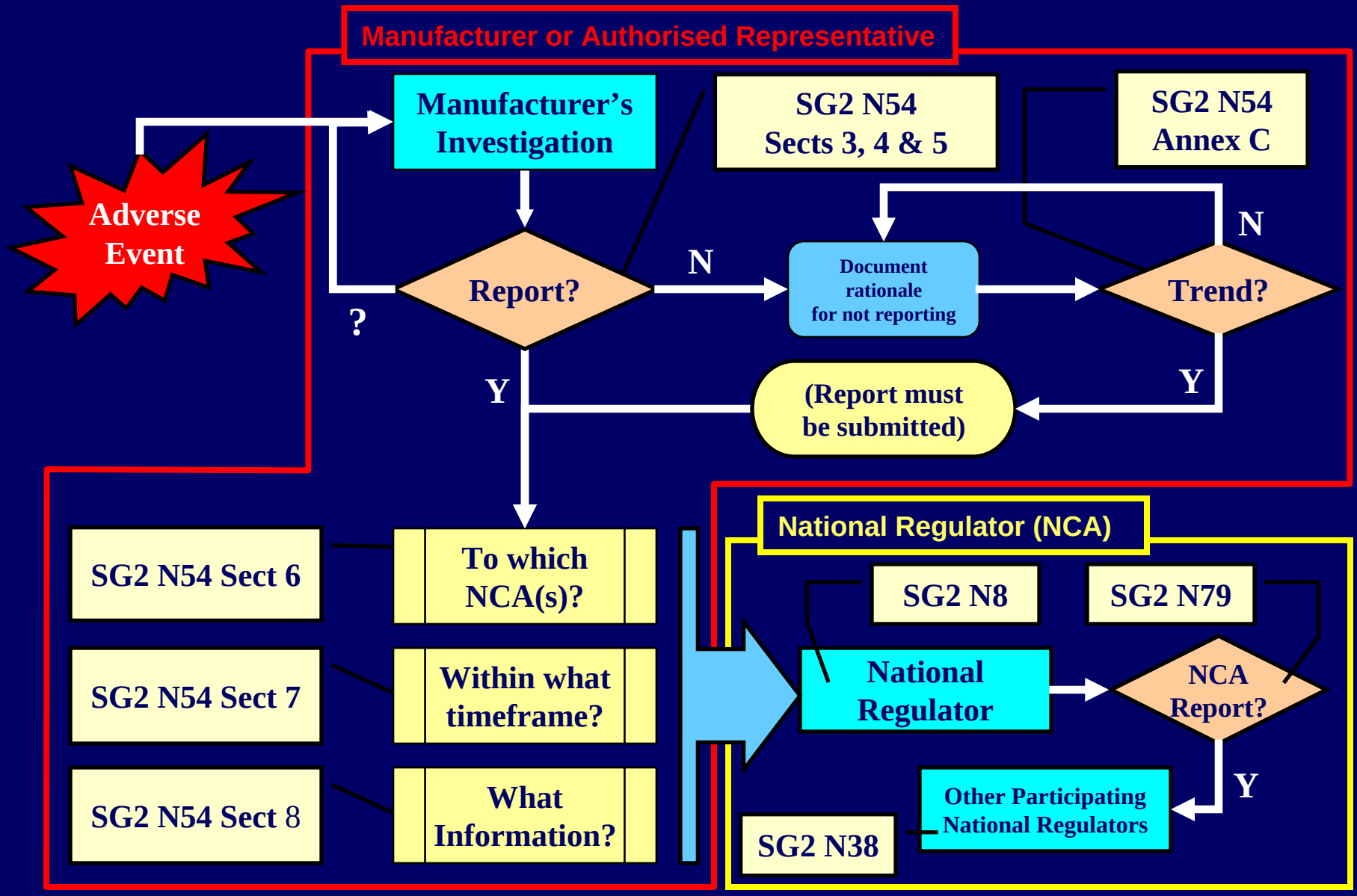
- SG2-N8R4: Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices
- SG2-N9R11: Global Medical Device Competent Authority Report
- SG2-N20R10: National Competent Authority Report Exchange Criteria
- SG2-N38R14 Application Requirements for Participation in the GHTF National Competent Authority Report Exchange Program.

GHTF SG2 N79R8

SG2 Guidance
Other documents & guidance

- SG2-N6R3: Comparison of the Device Adverse Reporting Systems in USA, Europe, Canada, Australia & Japan
- SG2-N16R5: SG2 Charge & Mission Statement
- SG2-N12R4: Précis
- SG2-N47R4: Review of Current Requirements Regarding Post-market Surveillance
- SG2-N57R8: Content of Field Safety Notice
- SG2-N61R6: PMS Harmonisation Chart

Map of SG2 Guidance on AE Reporting



GHTF SG2 N54 :

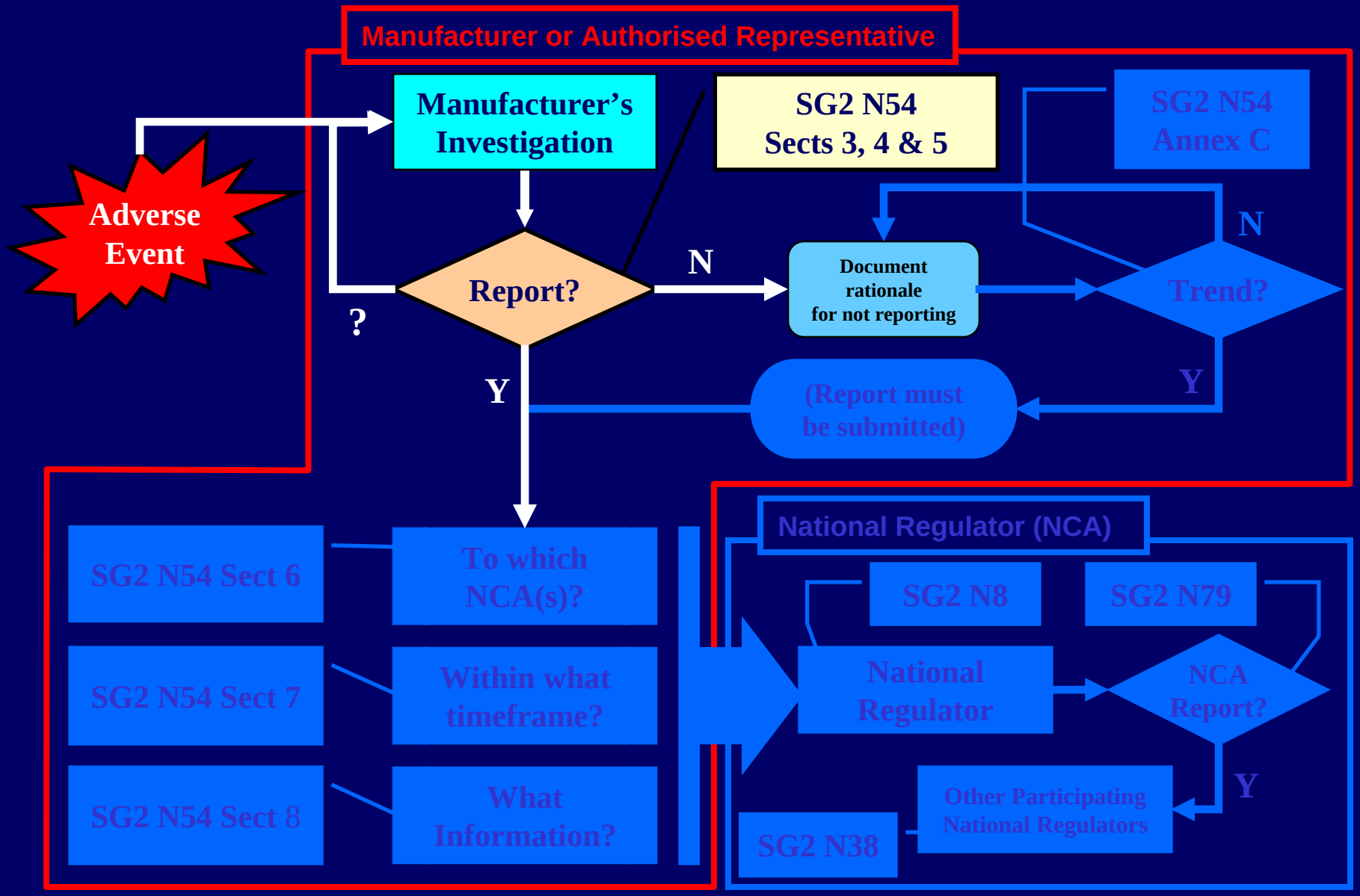
Table of Contents

- Section 1 Scope
- Section 2 Definitions
- Section 3 Adverse Event Reporting Guidance
- Section 4 Exemptions
- Section 5 Use error
- Section 6 To Whom to Report
- Section 7 Reporting Timeframes
- Section 8 Report Data Set

Annexes :

- A. Universal data set
- B. Timing of AE report
- C. Trends
- D. Use error

Reporting Criteria and Exemptions



GHTF N54 Section 3.0
Three Basic Reporting Criteria

- An EVENT must have occurred

AND

- The manufacturers device was ASSOCIATED with the event

AND

- The event led to the death or SERIOUS INJURY of a patient user or other person, OR might lead to death or serious injury if the event re-occurs

GHTF N54 Section 4.1- 4.8
Exemption Rules

Whenever any one of the following exemption rules is met, the adverse event does not need to be reported to a NCA by the manufacturer

Exemption Rules

1) Deficiency of a new device found by the user prior to its use
2) Adverse event caused by patient conditions
3) Service life or shelf life of the medical device
4) Malfunction protection operated correctly
5) Negligible likelihood of occurrence of death or serious injury
6) Expected and foreseeable side effects
7) Adverse events described in an advisory notice
8) Reporting exemptions granted by NCA

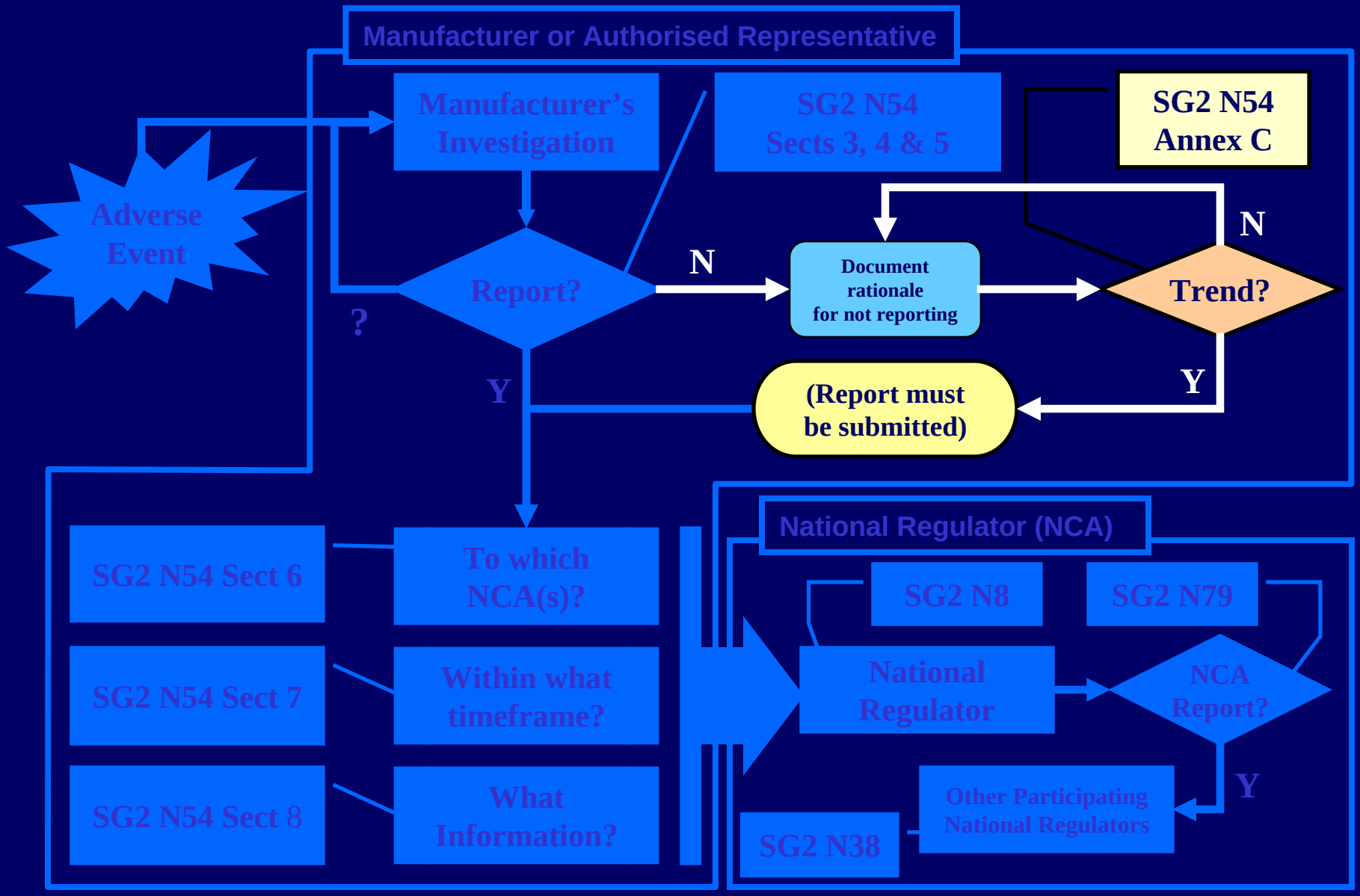
GHTF N54 Section 4
Other considerations

- If a NCA requires reporting a specific type of event due to a significant public health concern, the exemptions are no longer applicable
- Adverse events which are subject to an exemption become reportable to the NCA if a change in trend (usually an increase in frequency) or pattern is identified

Reporting of Use Errors and Abnormal Use

R=Report
NR*= No Report*

Trends

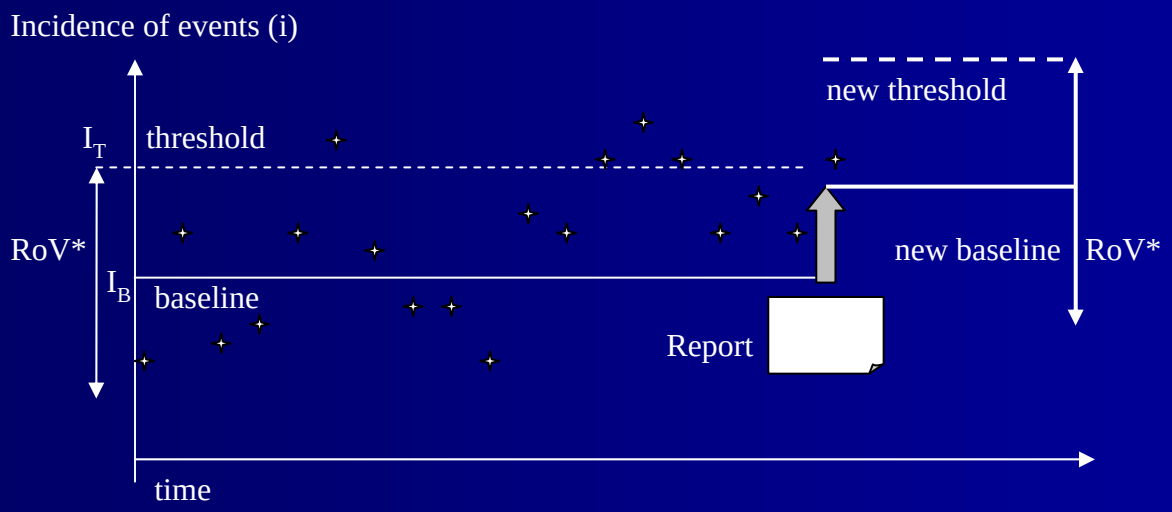

Manufacturer or Authorised Representative
Manufacturer's Investigation
SG2 N54 Sects 3, 4 & 5
SG2 N54 Annex C
Adverse Event
Report?
N
Document rationale for not reporting
Trend?
N
Y
(Report must be submitted)
?
Y
SG2 N54 Sect 6
To which NCA(s)?
SG2 N54 Sect 7
Within what timeframe?
SG2 N54 Sect 8
What Information?
National Regulator (NCA)
SG2 N8
SG2 N79
National Regulator
NCA Report?
Y
Other Participating National Regulators
SG2 N38

AE Trend Reporting

- Adverse events specifically exempted from reporting become reportable if there is a change in trend (usually an increase in frequency) or pattern is identified
- The SG2 document on trend reporting describes the criteria for identifying a significant increase in the rate of adverse events
- Not a handbook of statistical techniques
- Provides guidance to assist manufacturers to perform trending

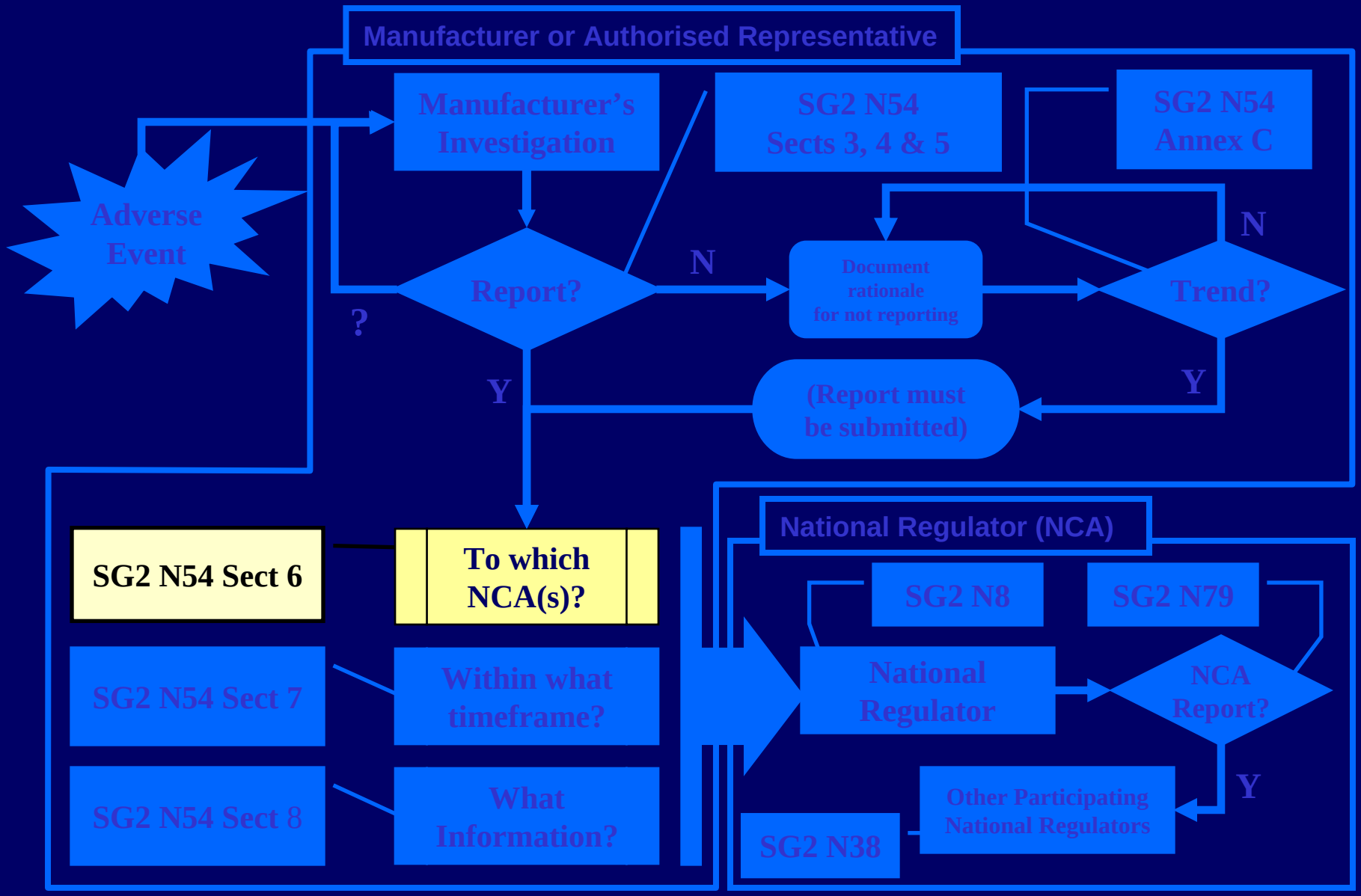
AE Trend Reporting

- Example of an upward shift in trend



* normal Range of Variance

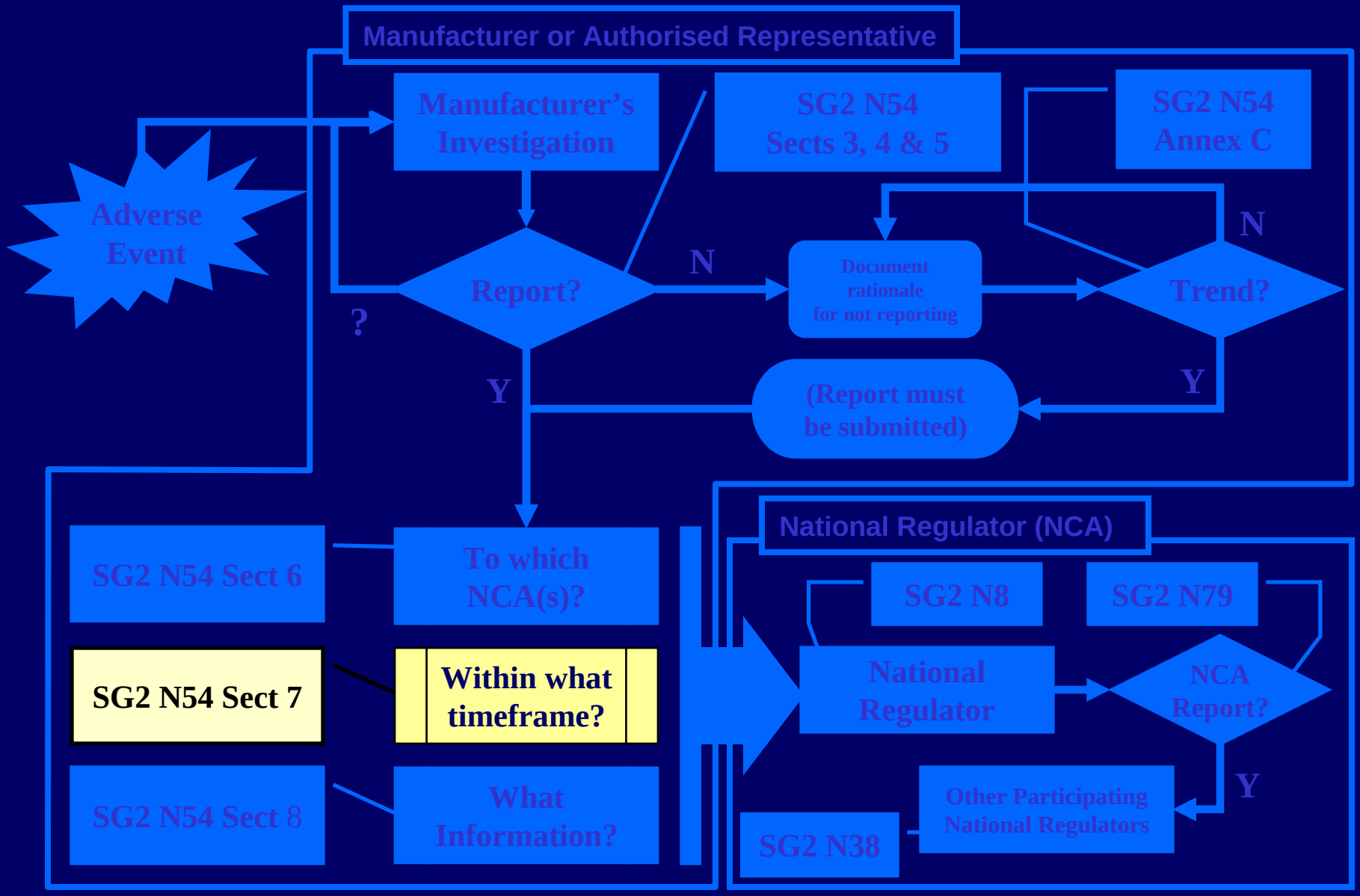
To Which NCAs to Report?



GHTF N54 Section 6
To Whom to Report

- Adverse Events must be reported to a National Competent Authority (NCA) according to applicable requirements in each jurisdiction. NCAs should provide a contact point to manufacturer from reporting
- SG2 considered several options that might resolve this situation, including the establishment of a global database for submission of adverse event reports

Within What Timeframe?



GHTF N54 Section 7 & Annex B
Reporting Timeframes

- Adverse events that result in unanticipated death or unanticipated serious injury or represent a serious public health threat must be reported immediately by the manufacturer
- All other reportable events must be reported as soon as possible by the manufacturer, but not later than 30-elapsed calendar days following the date of awareness of the event

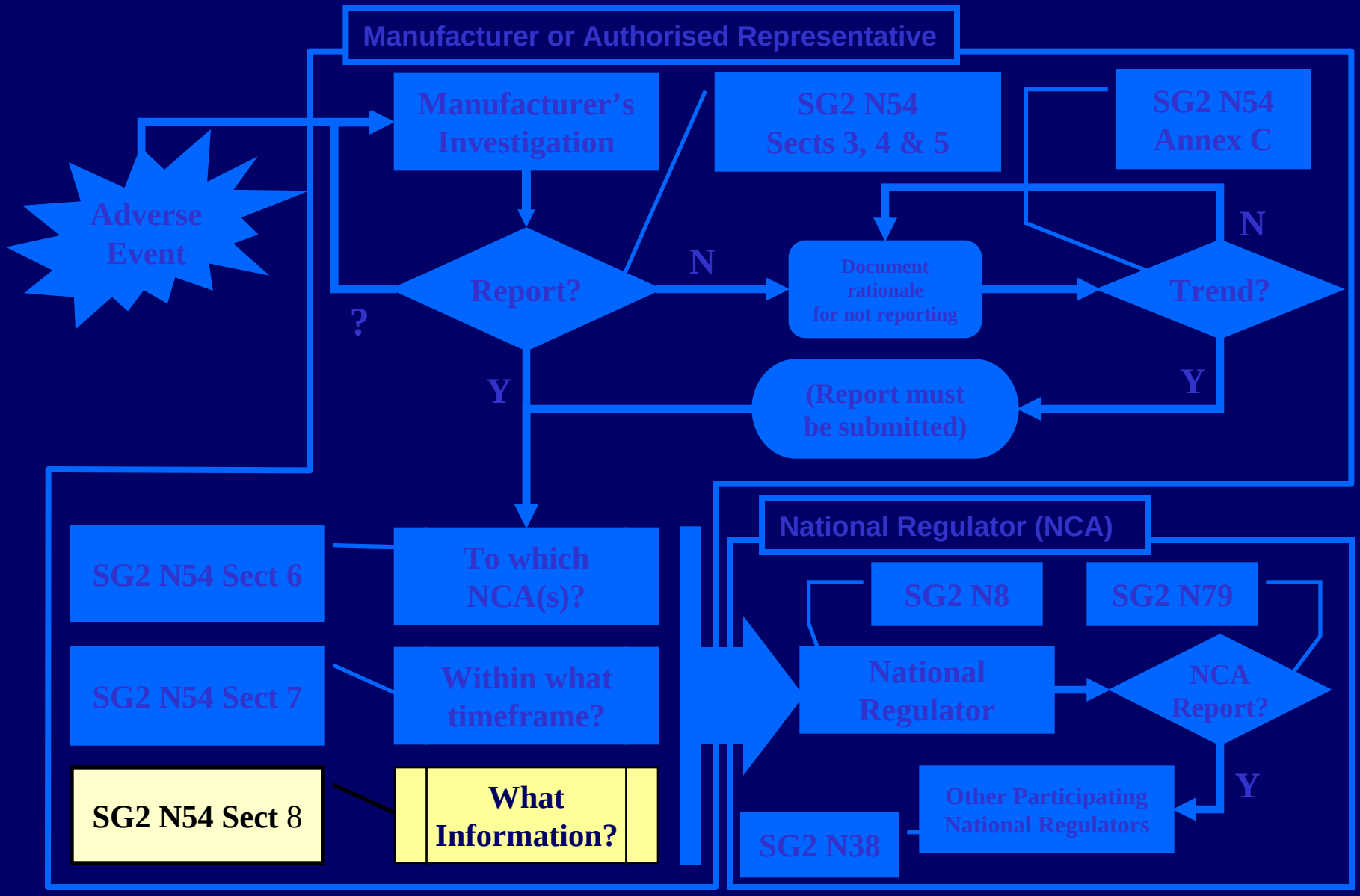
Reporting Timeframes

- Immediately: For purposes of adverse event reporting, immediately means as soon as possible, but not later than 10 elapsed calendar days following the date of awareness of the event
- Serious public heath threat: Any event type, which results in imminent risk of death, serious injury, or serious illness that may require prompt remedial action

Reporting Timeframes

- Unanticipated: A death or serious injury is considered unanticipated if the condition leading to the event was not considered in a risk analysis performed during the design and development phase of the device There must be documented evidence in the design file that such analysis was used to reduce the risk to an acceptable level

What Information (Dataset)?



Report Data Set

- Event information: Dates, Reporter details, Healthcare facility details, Patient details, Event type and description, Notified CA's, Resolution description
- Device Information: Manufacturer, Generic device group, Disposition, Results of analysis, Corrective action taken.
- Other: Comments, Notified Body details, CAs notified of Corrective action

What we've done so far…

Post-Market Surveillance

Post-market Surveillance Activities

Reference: GHTF SG2 N61R4

Market Surveys

Market Surveys of Technical and clinical documentation

Public Access to Information

Provide public access to information taken and reported to the Agency

Vigilance

Evaluate and investigate reported device problems and complaints

Recalls

Order, Monitor, and Classify product recalls, and disseminate written communications to appropriate recipients

Enforcement

Prohibit distribution via regulatory processes such as injunction, product seizure, import detention, etc.

Laboratory Testing

Testing of product for compliance with standards

Review of Product Claims / Labelling

Labelling includes labels, IFU, promotional material, websites

Technical File Reviews

Review of Clinical and Technical Information for a specific product

Condition of Approval Studies

Review of product - associated clinical trials

Standards Activities

Participate in global and international programs towards standardization and harmonization

Audits on Manufacturer

Inspect manufacturer processes and procedures for production and complaints handling

Other Post Market Feedback

Information on device performance in post-market phase (...ISO 13485)

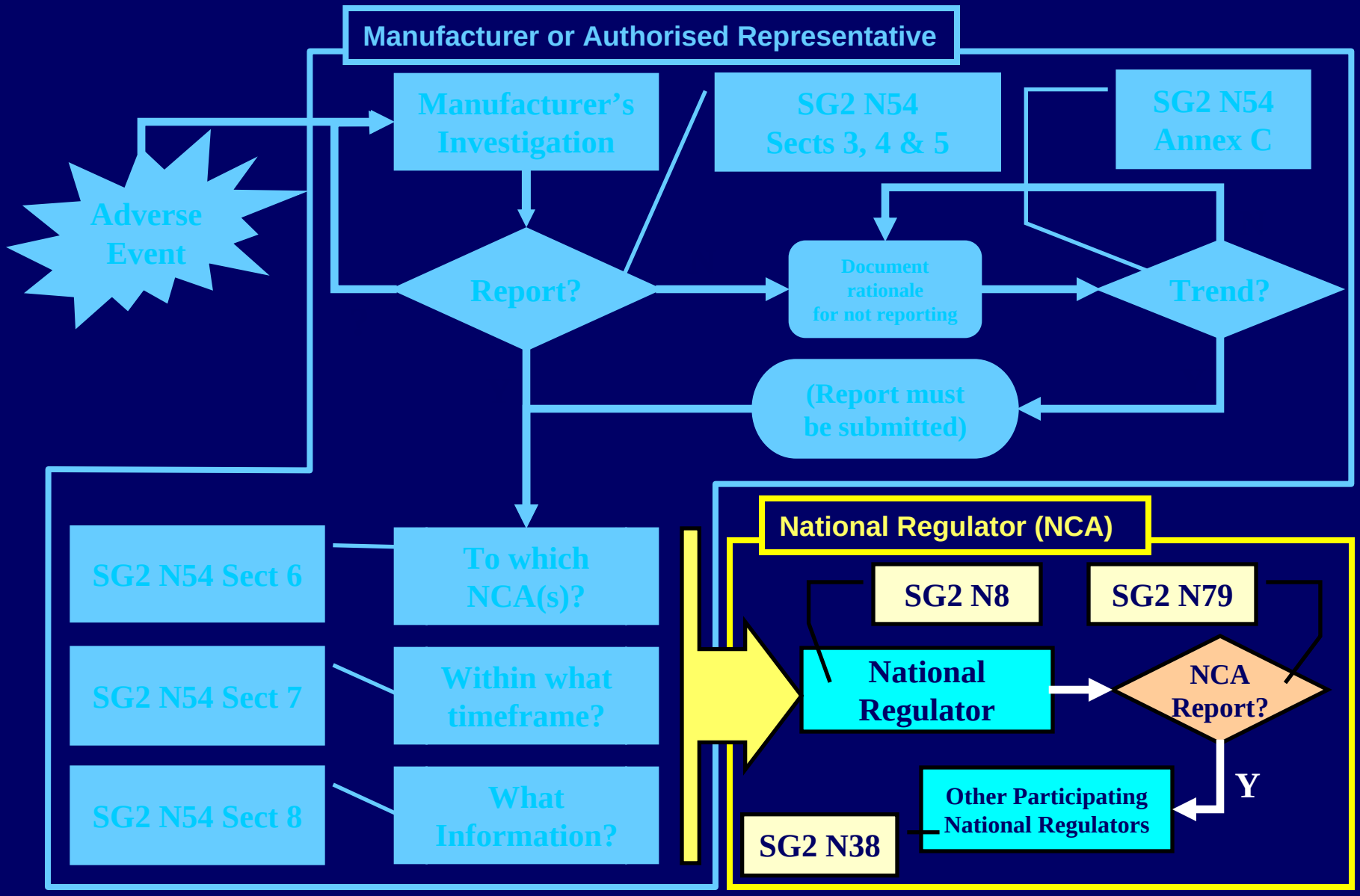
Summary of PMS Documents

- GHTF SG2 N47R5 Review of Current Requirements on Post-market Surveillance.
- GHTF SG2 N61R5 PMS Harmonization Chart
- GHTF SG2 N57R8 Harmonising the Content of Field Safety Notices.

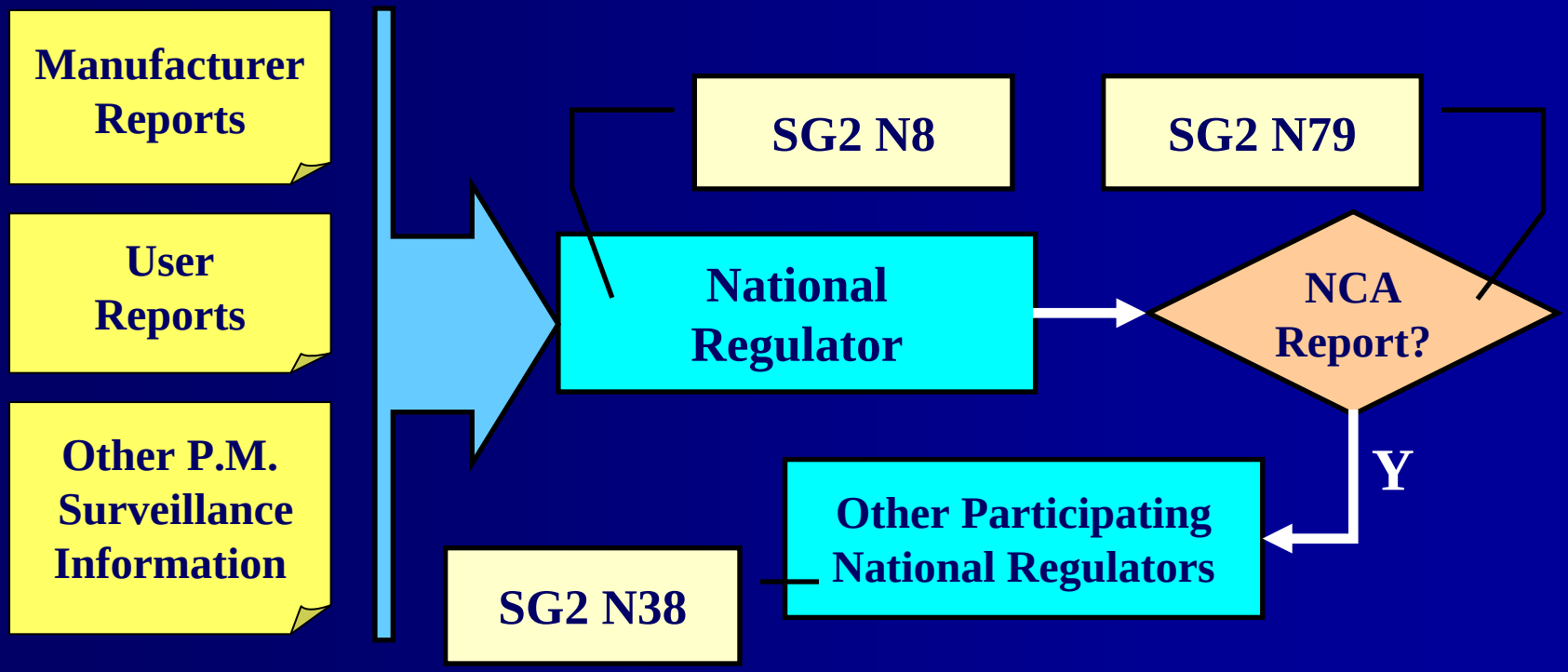
What we've done so far…

National Competent Authority Report Program

Map of SG2 Guidance on AE Reporting



Handling Adverse Event Reports:
NCA Systems



NCA Reports

- Are:
  - Reports that contain important information about an issue relating to a medical device that is or may be of great public health consequence.
- Are NOT:
  - SOLELY about Recalls or Safety Alerts
  - About individual adverse events
- May:
  - Contain information about issues that have not been completely resolved and which is therefore CONFIDENTIAL

Handling of Reports: Confidence

"A good reporting culture … can only be achieved through *confidence between all parties concerned*. The question will always remain; what happens to data handed into the system? Can everybody along the line be trusted? Will the information be properly treated? As important as confidential and discrete handling and treatment of data, will be the way conclusions are drawn. What information is to be released and used, and how will this be done."

NCAR
Hazards Associated with Reporting

- Public release of CONFIDENTIAL information
- Inappropriate release of information
- Misinterpretation of the issue
- Over-reaction to an issue
- Under-reaction to an issue

Participation:
Pre-requisites

Participant Level	Associate	Full
Type of Information Sought by Participant	Public	Confidential
Prerequisites		
Possible Admin. Charge	Yes	Yes
Working Reporting System	No	Yes
Training	Yes #	Yes *

Training regarding GHTF N9 and N20 only. * Full Training

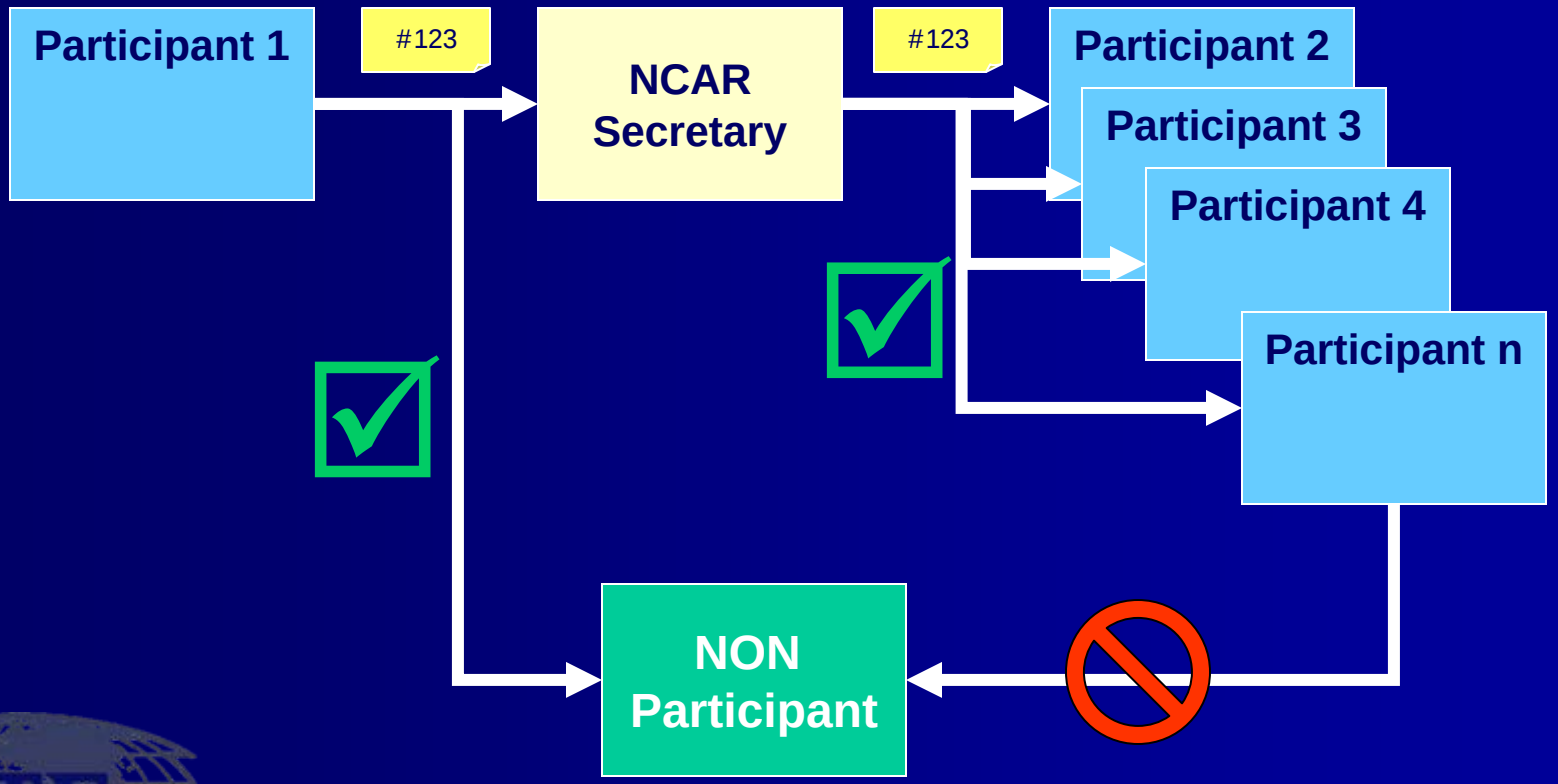
Participation:
Commitments

Participant Level	Associate	Full
Type of Information Sought by Participant	Public	Confidential
A commitment to:		
Confidentiality	No	Yes
Full Participation	No	Yes
Single Contact Point	Yes	Yes
Must be NCA	No	Yes

Participation:
Important Commitments

- Must treat reports labelled “Confidential” **STRICTLY CONFIDENTIAL**
- Must use form N79:
  - Ensures complete information
  - Prevents duplication
  - Protects sender
- Must not “send on” reports to non-participants.

Participation:
Sending to non participants



What we're planning to do…

Active/New Work Items

- Pilot on Electronic Reporting – N87
- New work item on the definition and classification of “Recalls” and associated actions
- New work item on the definition of the term “Adverse Event”

Monitoring & Improvement Phase:

- Maintenance of NCAR
  - Development and maintenance of training materials - Handling of new applications for membership/Training - Review of performance
- Monitoring of the performance of SG2 Guidance
  - Report on the implementation - Review and update documents
- Improvement of reporting and exchange mechanisms
  - Electronic reporting - Passive database
- Take on new work items as identified by developments in products and regulations.
  - IVDs - combination products - software devices – nanotechnology - Public access to information
- Training on SG2 Guidance

After that we'll "put our feet up"