Asia-Pacific
Economic Cooperation

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

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Annex: Presentation Slides, Toronto, Canada May 14 – 16, 2009

Life Sciences Innovation Forum
APEC Committee on Trade and Investment

August 2009

CTI 22/2008T

Prepared by
Jeffrey L. Gren
U.S. Department of Commerce, International Trade Administration
1401 Constitution Avenue, Suite 1015
Washington, DC 20230
USA

Produced for:
Asia Pacific Economic Cooperation Secretariat
35 Heng Mui Keng Terrace Singapore 119616
Tel: (65) 6891 9600 Fax: (65) 6891 9690
Email: info@apec.org Website: www.apec.org

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Asia-Pacific Economic Cooperation

MEDEC
CANADA'S MEDICAL DEVICE TECHNOLOGY COMPANIES
LES SOCIÉTÉS CANADIENNES DE TECHNOLOGIE DES DISPOSITIFS MÉDICAUX

Agenda APEC Funded GHTF Latin America Regulatory Harmonization Training Program
Toronto, Canada, May 14 - 16, 2009

Thursday, May 14th, 2009 – Toronto Westin Hotel	
11:00am – 2:00pm	Registration Desk Opens
1:00pm – 3:30pm	APEC Funded GHTF Training Seminar Opening Plenary Pier 4 & 5, Westin Hotel
1:00pm – 1:10pm	Welcome and Program Overview - **Jeffrey Gren, Project Overseer and Director, Office of Health and Consumer Goods, U.S. Department of Commerce, Manufacturing and Services**
1:10pm – 1:40pm	Overview of the Global Harmonization Task Force (GHTF), Role of GHTF Study Groups, and Future GHTF Activities - **Roland Rotter, GHTF Steering Committee Chair**
1:40pm – 2:40pm	**Panel Discussion:** "The role of regulators, industry, and distributors in global medical device regulatory harmonization and the integrity of the medical device supply chain" Moderator: Jeffrey Gren, Director, Office of Health and Consumer Goods, U.S. Department of Commerce Panel Members: **Meghal Khakhar, Manager, Regulatory and Scientific Affairs , Baylis Medical, Canada** **Petra Kaars-Wiele, Director International Regulatory Affairs/Affiliate Compliance, Abbott Laboratories, Germany** **Miang Chadaporn Tanakasemsub, Regional Regulatory Affairs Director, Asia, Bausch & Lomb Ltd., Hong Kong**
2:40pm – 3:40pm	Special Session - Study Group 5 (Clinical Safety/Performance) Dr. **Greg Leblanc**, MEDEC and Cook Canada
6:00 pm	Buses depart Westin Hotel for Humber College **(available only on May 14)**

Friday, May 15th, 2009 – Humber College		
7:30am – 9:00am	Registration Desk Open Main Floor, Guelph-Humber Building, Humber College	
7:00am 8:00am	Breakfast for participants staying at Humber College Cafeteria, Student Residence, Humber College	
Breakout Sessions – Seminar attendees will be divided into two smaller groups (Group A and Group B) to facilitate discussion and interaction.		
	Group A **GH111, Guelph-Humber Building, Humber College**	**Group B** **GH117, Guelph-Humber Building, Humber College**
8:30am – 10:15	**Study Group 1 Training (Premarket Evaluation)** Ms. **Maria Carballo**, Health Canada Dr. **Petra Kaars-Wiele**, European Diagnostic Manufacturers Association (EDMA) and Abbott Mr. **Michael C. Morton**, AdvaMed and Medtronic Ms. **Brenda Murphy**, MEDEC and SciCan	**Study Group 4 Training (Auditing)** Mr. **Armand Tsai**, Health Canada Mr. **Albert Li**, Industrial Technology Research Institute (Chinese Taipei)
10:15am - 10:30am	Coffee Break	
	Group A	**Group B**
10:30am – 12:15pm	**Study Group 1 Training (Premarket Evaluation)**	**Study Group 4 Training (Auditing)**

12:15pm – 1:15pm	Lunch	
	Group A **GH111, Guelph-Humber Building, Humber College**	**Group B** **GH117, Guelph-Humber Building, Humber College**
1:15pm – 3:00pm	**Study Group 2 Training (Post-market Surveillance/Vigilance)** Dr. **Ekkehard Stoesslein**, BFARM, (Germany) Mr. **Philippe Auclair**, EUCOMED and Abbott Vascular	**Study Group 3 Training (Quality Systems)** Mr. **Egan Cobbold**, Health Canada Mr. **Gunter Frey**, National Electrical Manufacturers Association (NEMA) and Philips Healthcare
3:00pm – 3:15pm	Coffee Break	
	Group A	**Group B**
3:15pm – 5:00pm	**Study Group 2 Training (Post-market Surveillance/Vigilance)**	**Study Group 3 Training (Quality Systems)**
7:30pm – 10:30pm	**Hospitality Dinner (Summary and Closing Remarks)** **7th Semester, Building L-M, Humber College**	
Saturday May 16th, 2009 – Humber College		
7:00am – 8:00am	Breakfast for participants staying at Humber College Cafeteria, Student Residence, Humber College	
	Group A **GH111, Guelph-Humber Building, Humber College**	**Group B** **GH117, Guelph-Humber Building, Humber College**
8:30am – 10:15	**Study Group 3 Training (Quality Systems)**	**Study Group 2 Training (Post-Market Surveillance/Vigilance)**
10:15am - 10:30am	Coffee Break	
	Group A	**Group B**
10:30am – 12:15pm	**Study Group 3 Training (Quality Systems)**	**Study Group 2 Training (Post-Market Surveillance/Vigilance)**
12:15pm – 1:15pm	Lunch	
	Group A **GH111, Guelph-Humber Building, Humber College**	**Group B** **GH117, Guelph-Humber Building, Humber College**
1:15pm – 3:00pm	**Study Group 4 Training (Auditing)**	**Study Group 1 Training (Premarket Evaluation)**
3:00pm – 3:15pm	Coffee Break	
	Group A	**Group B**
3:15pm – 5:00pm	**Study Group 4 Training (Auditing)**	**Study Group 1 Training (Premarket Evaluation)**
500pm	**Training Seminar Concludes**	

Humber College
Guelph-Humber Building
203 Humber College Boulevard
Toronto, Ontario M9W 6V3
Phone: (416) 675.6622

From Humber College Boulevard use the driveway marked ‘A’. This will get you closest to the Guelph-Humber Building where the APEC training is taking place.

The Global Harmonization Task Force: Overview and Status

Dr. R.G. Rotter
Chair of GHTF
and
Director, Medical Devices Bureau
Health Canada

Objectives

- Overview of the GHTF
  - History
  - Purpose
  - Structure and activities
  - Accomplishments
  - Strategic goals
  - The Future

Overview

- Informal grouping of medical device regulators and industry
- Began in 1992 with Canada, European Union, Japan, USA and Australia as founding members
- Currently consists of a Steering Committee, 5 Study Groups and several Ad Hoc Groups
- Has links with several partners, including: ISO, IEC, WHO, PAHO, AHWP

Overview

- Working to reduce or eliminate technical differences in regulatory requirements and practices
- GHTF conferences and commenting ondraft guidance documents
- Participation is broadening
  - “Participating Members”
  - “Observers”

Purpose

- 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

and

- To serve as an information exchange forum through which countries with medical device regulatory systems can benefit from the experience of other members.

Basic Principles

- 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
  - Wasteful for governments and industry
  - Delays technologies to the patient bedside

Organizational Structure

Steering Committee

- Provides policy direction and strategic planning, and assigns and oversees technical work initiatives
- Chair rotates between regions every three years
  - Regulator chair; industry vice-chair
  - Chair provides Secretariat
- US FDA (CDRH) maintains the GHTF website and records
- Meets twice/year and regular bi-monthly conference calls
- Operates by consensus

Study Groups

- Work plans approved by Steering Committee
- Volunteer experts appointed by Founding Member national regulators and industry associations
- Meet face-to-face 2-3 times/year
  - Work by E-mail between meetings

Study Groups

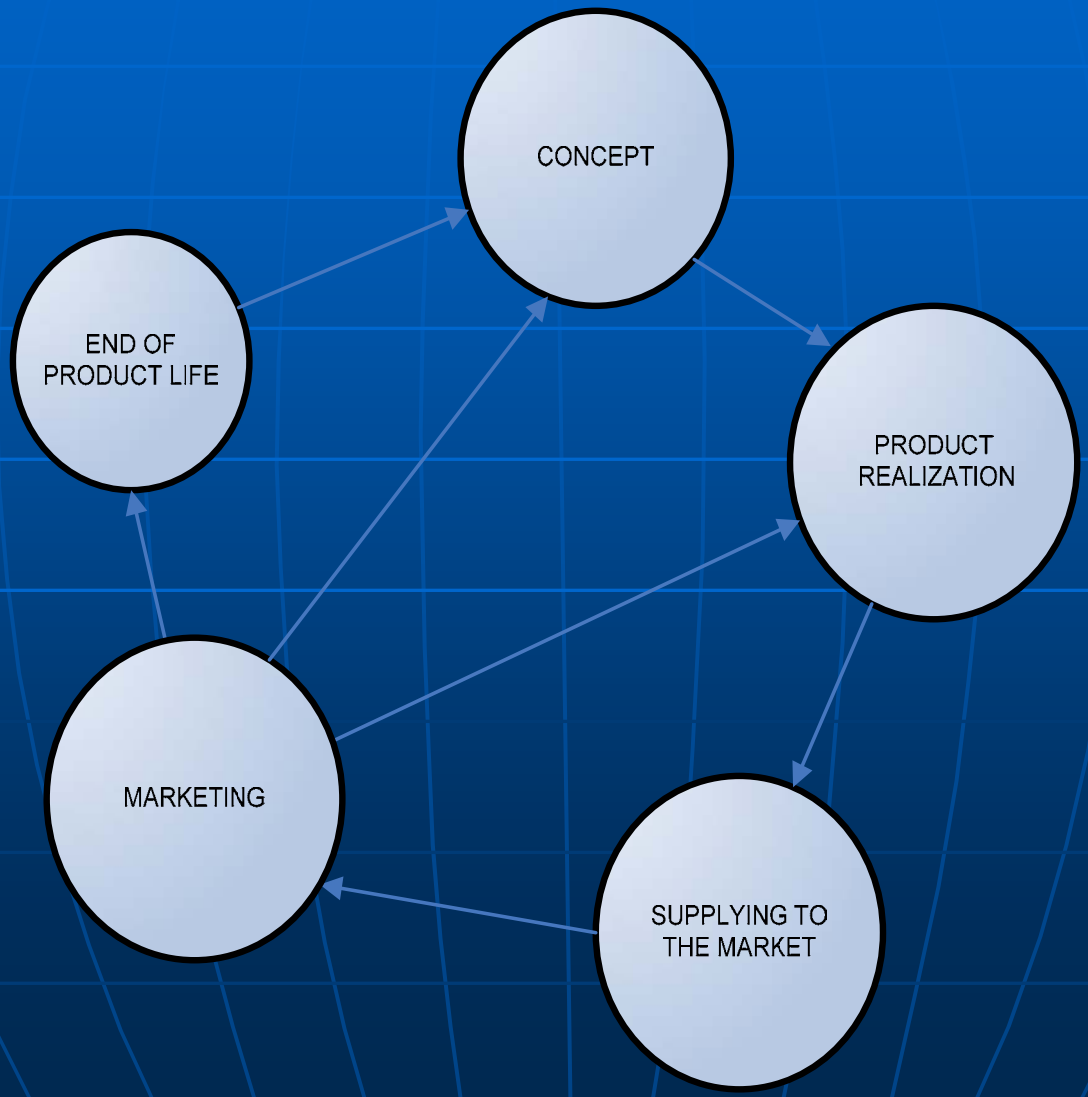
Study groups are the engine of GHTF guidance development (almost 40 posted)

- SG1: Premarket conformance
- SG2: Postmarket vigilance/surveillance
- SG3: Quality Systems
- SG4: Auditing
- SG5: Clinical effectiveness

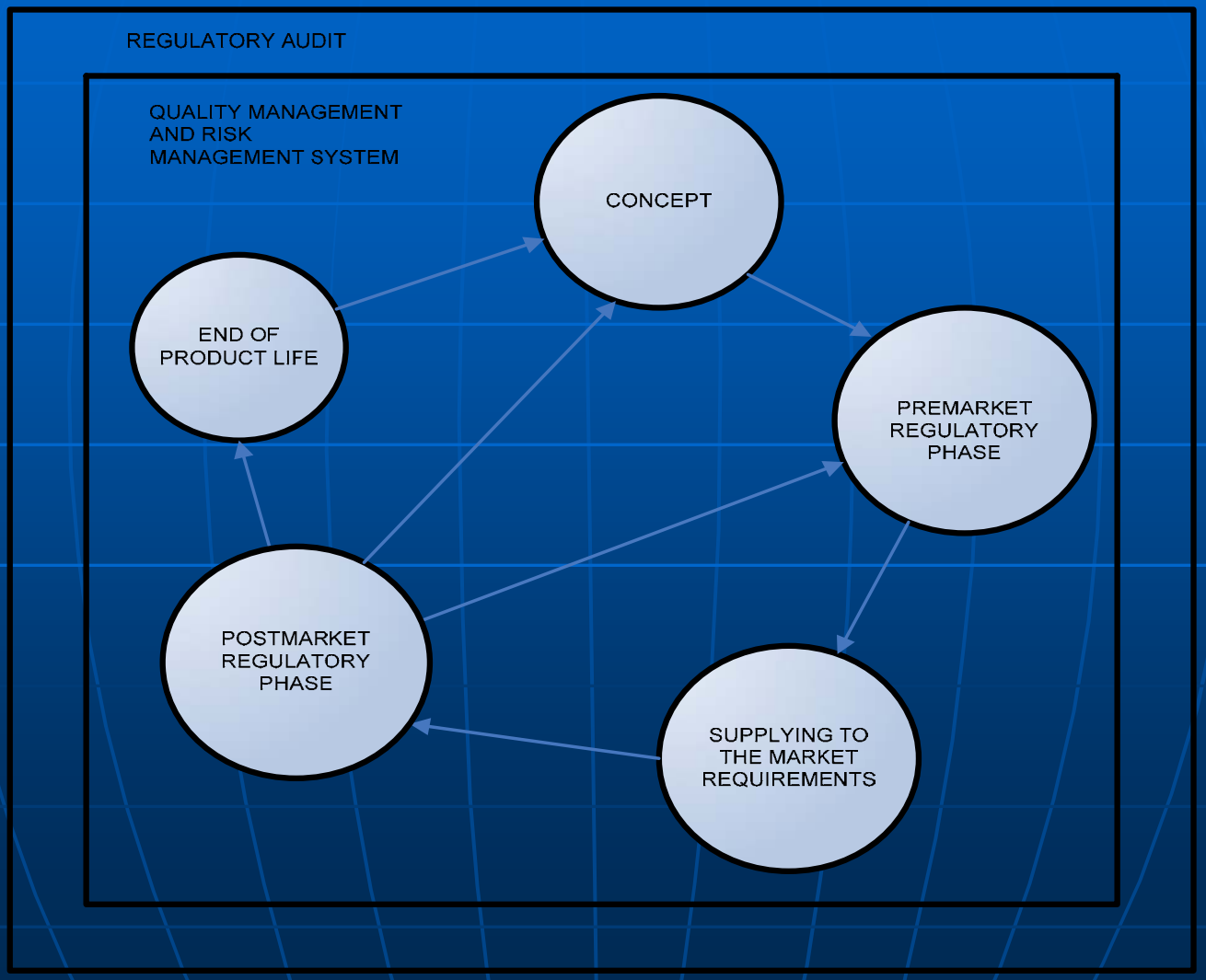
Special Topics: Ad Hoc Working Groups

- Medical device software
- Combination Products
- Training
- Global Regulatory Model
- Global Medical Device Nomenclature
- Unique Device Identifiers
- GHTF Administrative processes

Life Cycle


CONCEPT
PRODUCT REALIZATION
SUPPLYING TO THE MARKET
MARKETING
END OF PRODUCT LIFE

Regulatory Aspects



GHTF Areas of Activity

- Classification system and vocabulary
- Technical (science) requirements
- Format and content of marketing applications
- Assessment and review practices
- Post-market activities
- Quality Management Systems requirements and audits
- International standards

Guidance Documents

Study Group documents are:

- Developed by consensus
- Posted on GHTF website at proposed and final stages
- Public comments sought
- Represent consensus view of good regulatory practices
- No legal force or compulsion to adopt
- Implemented through local legal / regulatory processes
  - Typically adapted to suit local legal system and administrative resources and traditions

Strategic Goals

- Emerging regulatory challenges
- Implementing guidance documents
- Mutual acceptance of common data by regulators
- Evolving regulatory systems
- Communications
- Organization/infrastructure

Accomplishments To Date

- Risk-based classification system
- Common definitions and vocabulary
- Global Medical Device Nomenclature
- Technical (science) requirements
- Format and content of marketing applications (STED)
- Assessment and review practices
- Post-market activities
- Quality Management Systems requirements and audits
- Use of international standards

GHTF Successes To Date

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

Taking the Task Force Forward

- Expansion
- Guidance Implementation
- New Challenges

Expansion

- Work with AHWP, Latin American Countries, ISO, IEC and others who share the GHTF goals
- GHTF Training Plan
  - Invitation has been extended inviting organizations to become training partners
  - Continue to work with APEC on training
- Involve other countries
  - Translate guidance documents into other languages
  - Join National Competent Authority Report system (NCAR)
  - Adopt guidance with feedback to GHTF

Implementation

- Implementation of guidance documents
  - Direct adoption of documents by regulatory authorities
- Single QS audits used for multiple jurisdictions
  - Canada-Australia
  - Canada-USA Pilot
- Improve operation and expand membership of NCAR
- Adoption of GHTF Model as the regulatory framework for certain Asia economies

New Challenges

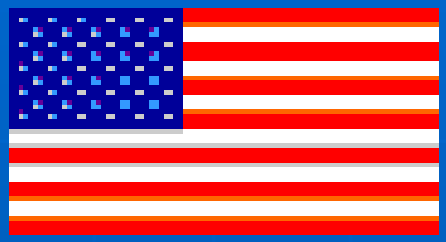
- Definition and regulation of “combination products”
- Training strategy for countries with no regulatory framework
- Expanded participation
  - Asia Harmonization Working Party
  - Latin American Harmonization WP
  - ISO
  - IEC
  - WHO
- Additional elements of global regulatory model
- Global Medical Device Nomenclature system

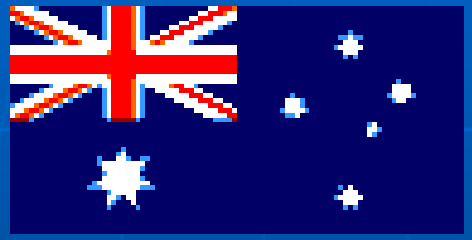
GHTF Model

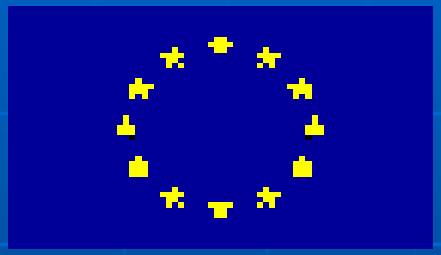
- Guidance documents available in English on the GHTF website: *www.ghtf.org*
- Links provided to translated documents
  - PAHO translated into Spanish and Portuguese
- Training on the GHTF model and guidance documents
  - APEC sponsored
  - Training Partners Initiative

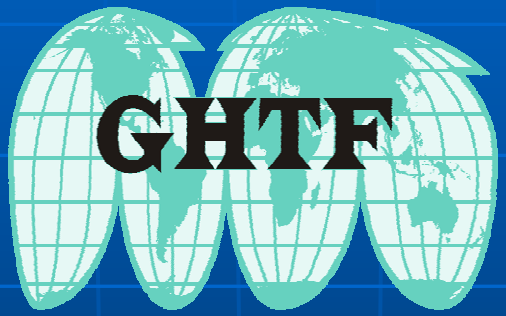
The Future is Now

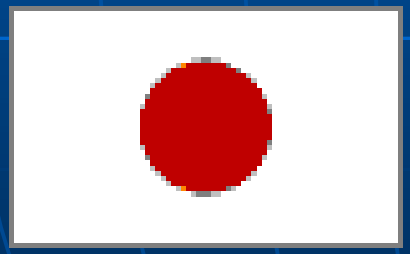
- The GHTF has accomplished much
- The time has come to build on this foundation and truly move toward the realization of <u>global harmonization</u>











Thank you

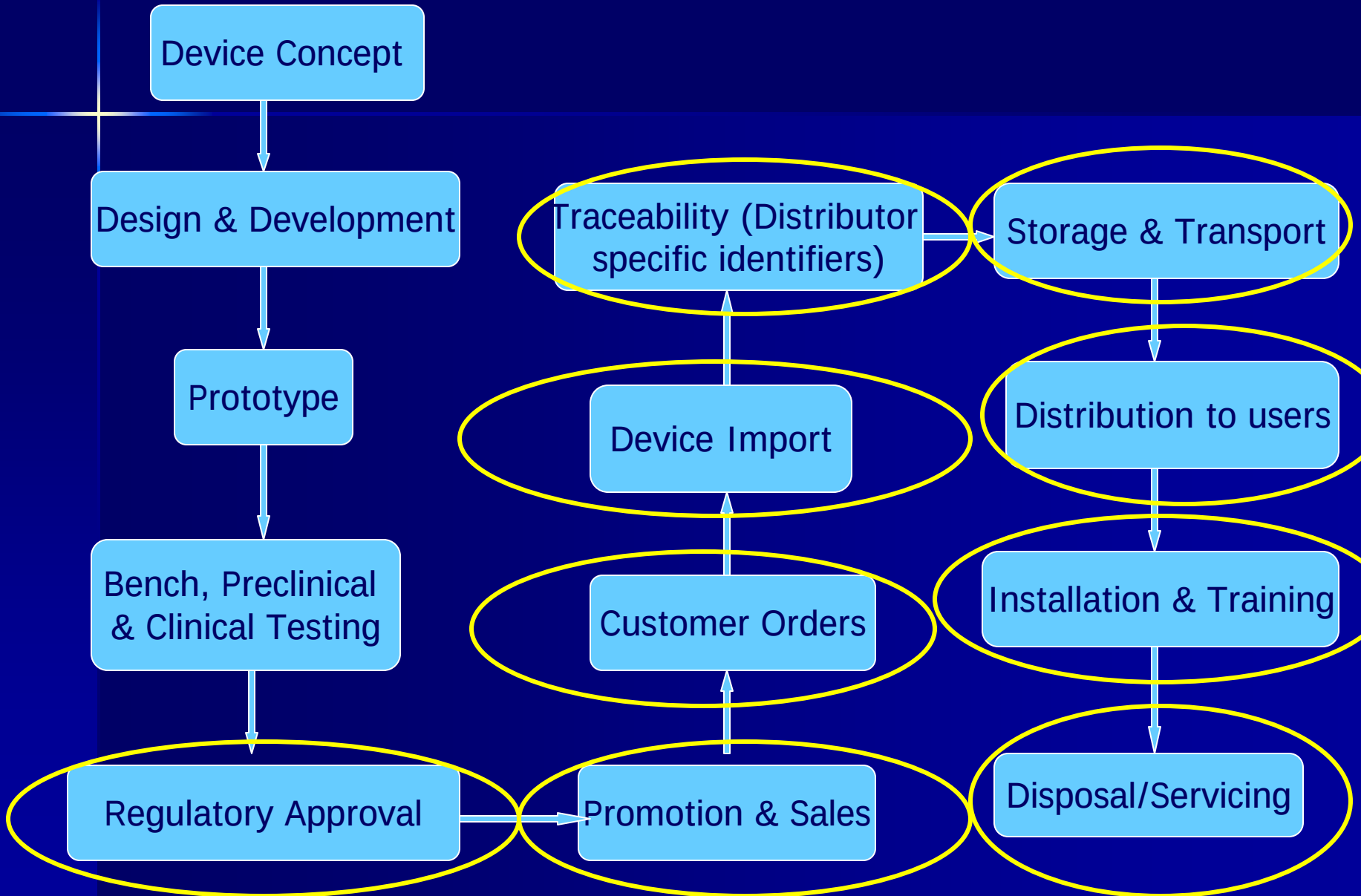
Role of Distributor in Global Harmonization and Integrity of Medical Device Supply Chain

Dr. Meghal Khakhar
MEDEC & Baylis Medical
14 May, 2009

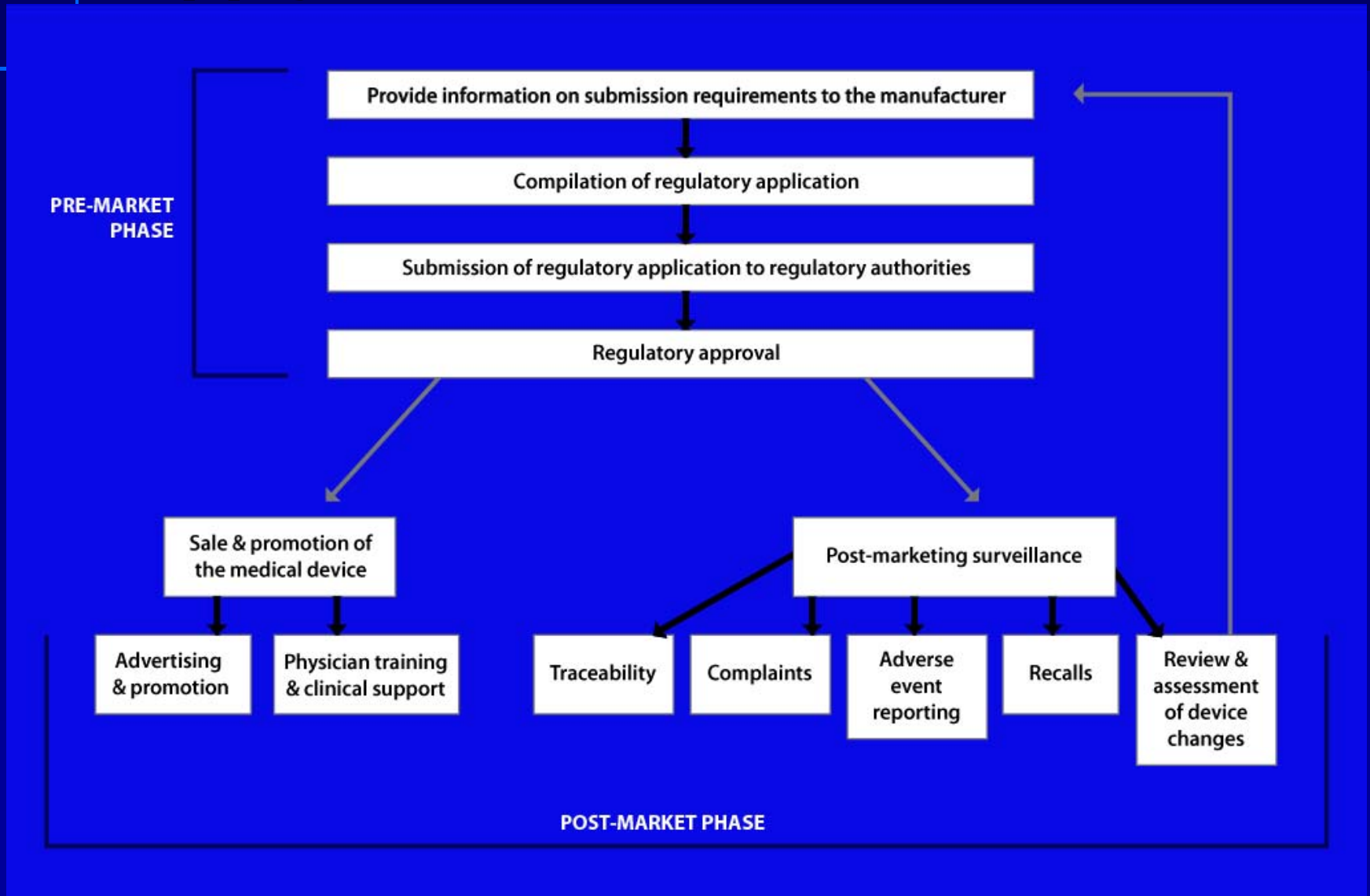
Presentation Outline

- Role of distributor:
  - Medical Device Supply Chain
  - Harmonization
- Harmonization - Challenges

Medical Device Supply Chain



Regulatory Role of the Distributor in Medical Device Supply Chain



Medical Device Supply Chain: Regulatory Role of the Distributor

- Legal responsibility for the safety and performance of the device throughout distribution chain
- Responsible for medical device approval and continued regulatory compliance in the respective jurisdiction
- Corresponds with the regulatory authority on behalf of the manufacturer
- Provides feedback collected from the field on device performance to the manufacturer

Harmonization - Role of the Distributor

- Knowledge of regional regulatory requirements and GHTF activities
- Instrumental in deploying the harmonized approach to several manufacturers
- Assist the manufacturer to submit the regulatory application in harmonized format (STED plus regional requirements)
- Be conscious of the level of change required for the manufacturer to implement the regional and harmonization requirements into their quality system
- Maintain effective communication with the manufacturer

Harmonization - Challenges in Pre-Market Phase

- Different country specific requirements
  - Regulatory philosophy including risk based classification
  - requirement for approval from FDA/EU/country of origin
  - requirement for testing the devices (development of standards)
  - material requirements
  - labelling requirements, etc.
  - difference in submission format by the manufacturer
- Difference in timelines of implementation of harmonized requirements
  - E.g. EN 60601 standard, DEHP and BPA requirement

Harmonization - Challenges in Post-Market Phase

- Different adverse event reporting timelines & definitions of “recall” for different jurisdictions
- Lack of communication between distributor and manufacturer: prevents timely submission of adverse event reports and recall notifications

Summary & Discussion

- Role of distributor:
  - Medical Device Supply Chain
  - Harmonization
- Harmonization - Challenges

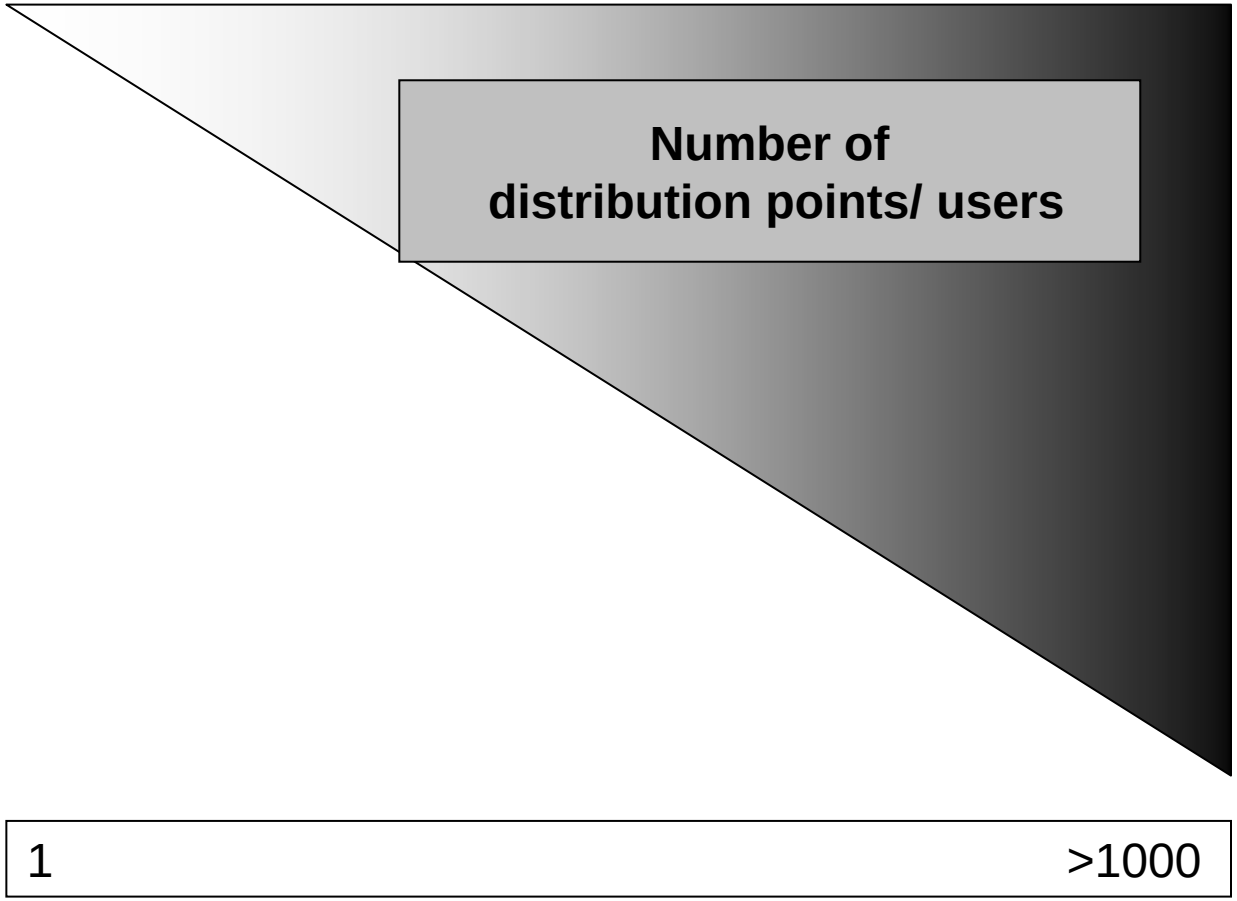
Legislation, Regulators
and
the safety of the distribution chain

Jos Kraus

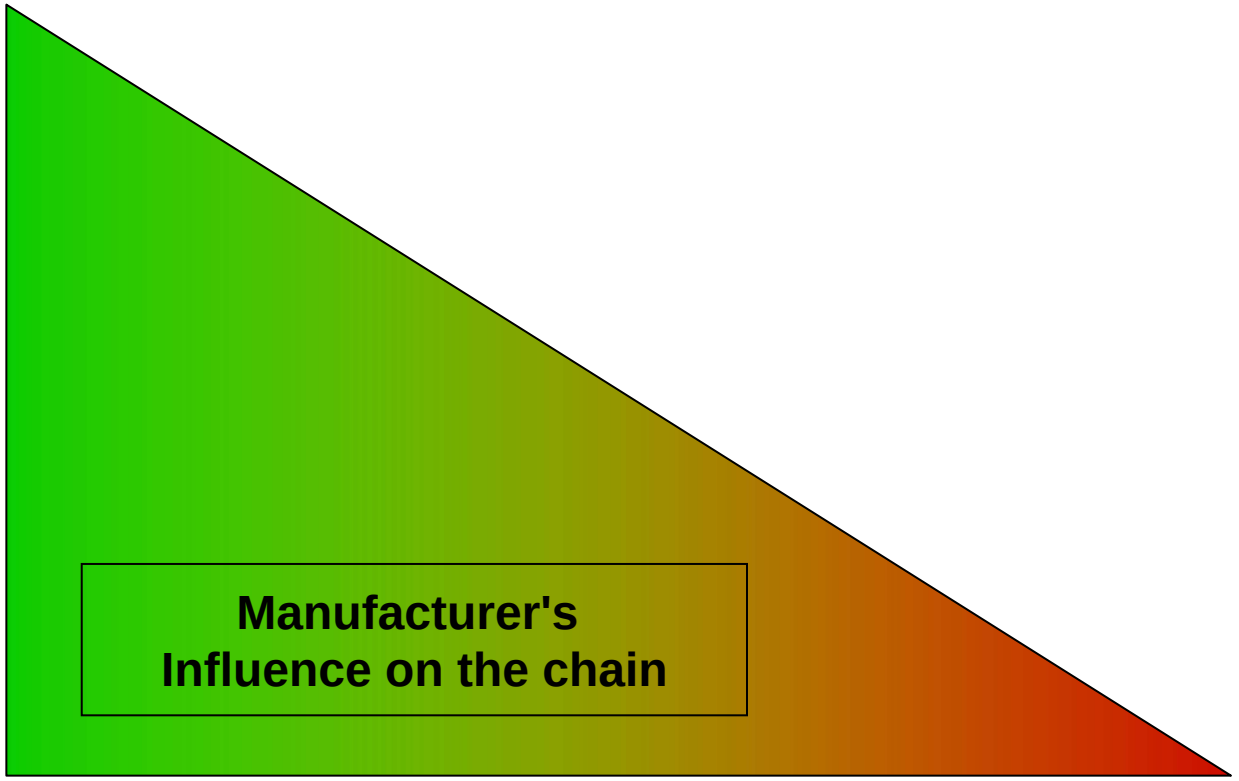
Inspectorate of health care

The Netherlands

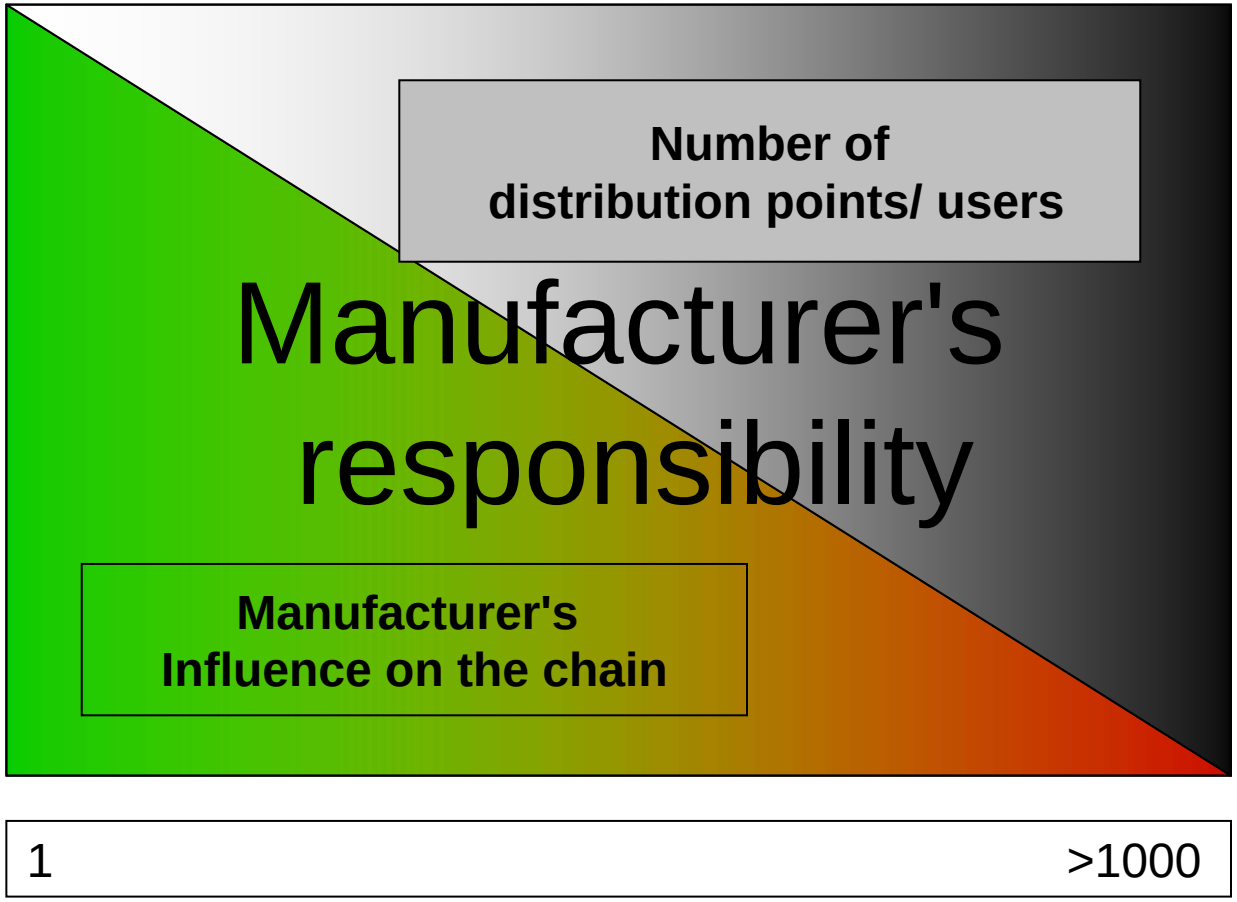
Number of entities



Manufacturer’s influence on the chain



Practice


Number of
distribution points/ users
Manufacturer's
responsibility
Manufacturer's
Influence on the chain
1
>1000

Europe versus USA

Europe

- Important historical roots
- **Open borders**
- Post Market emphasis on
  - Vigilance
  - Post marketing system
- Importers, distributors
  - Recently in regulation defined

USA

- There are differences between some States
- **Closed borders**
- Pre Market system
  - PMA
  - 510 K
- Establishment registration

What are the real motives?

- Purpose of the legislator:
  - Public Health
    - Patient safety
      - “Active or reactive” legislation
    - Vigilance
    - PMS
    - Medical Doctors
  - Trade
    - Unemployment
    - Local industry
  - Tax income
    - Import tax
    - VAT
  - Cost of Health Care

The role of regulators, industry, and distributors in global medical device regulatory harmonization and the integrity of the medical device supply chain

Miang Tanakasemsub
Co-Chair AHWP TC WG02

Bausch & Lomb

Common stage of Medical Device regulation

Figure 2. Persons who directly manage the different phases of medical devices

WHO: MEDICAL DEVICE REGULATIONS: *Global overview and guiding principles*

Supply/Distribution Chain Control

- Overview of regulatory controls
  - To ensure quality of medical device is maintained throughout distribution chain
  - To ensure systems are in place for
    - Proper packaging and storage
    - Documentation of supply and distribution
    - FSCA reporting system
    - Adverse event assessment and reporting
    - Advertisement and promotion
      - Prohibition on false or misleading advertisement

Asia Pacific Industry Challenges

- Distributors business models
- Quality of distributors??
- Awareness of local industry
- Unavailability of global standard/GHTF guidance documentation for supply/distribution control
- Individual development of Good practice in the region
  - Korea GIP
  - Singapore GDPMDS
  - Thailand GIP development
  - Malaysia QS for importer/distributors development
  - More coming

Thank you

Bausch & Lomb

Global Harmonization Task Force Study Group 5

Greg LeBlanc
Vice Chair, GHTF SG5

March 2009

COOK® MEDICAL

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

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 “proposed” documents
    - *Clinical Investigation- GHTF SG5/N3 (to be finalised shortly)*
    - *Post-market Clinical Follow-up SG5/N4 (out for public comment, est:Q4 2009)*
  - Memorandum of Understanding with ISO TC 194 (responsible for ISO 14155) – close liaison necessary to avoid overlap

Current Status

- Work In Progress:
  - Clinical Evaluation for IVDs (with SG1)
  - Adverse Event Reporting in Clinical Investigations (with SG2)

SG5 – N1 – Definitions and Concepts Document

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

Definitions and Concepts Document - 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.
- Clinical Evidence:
  - The clinical data and the clinical evaluation report pertaining to a medical device.

SG5 – N2 – Clinical Evaluations Document

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

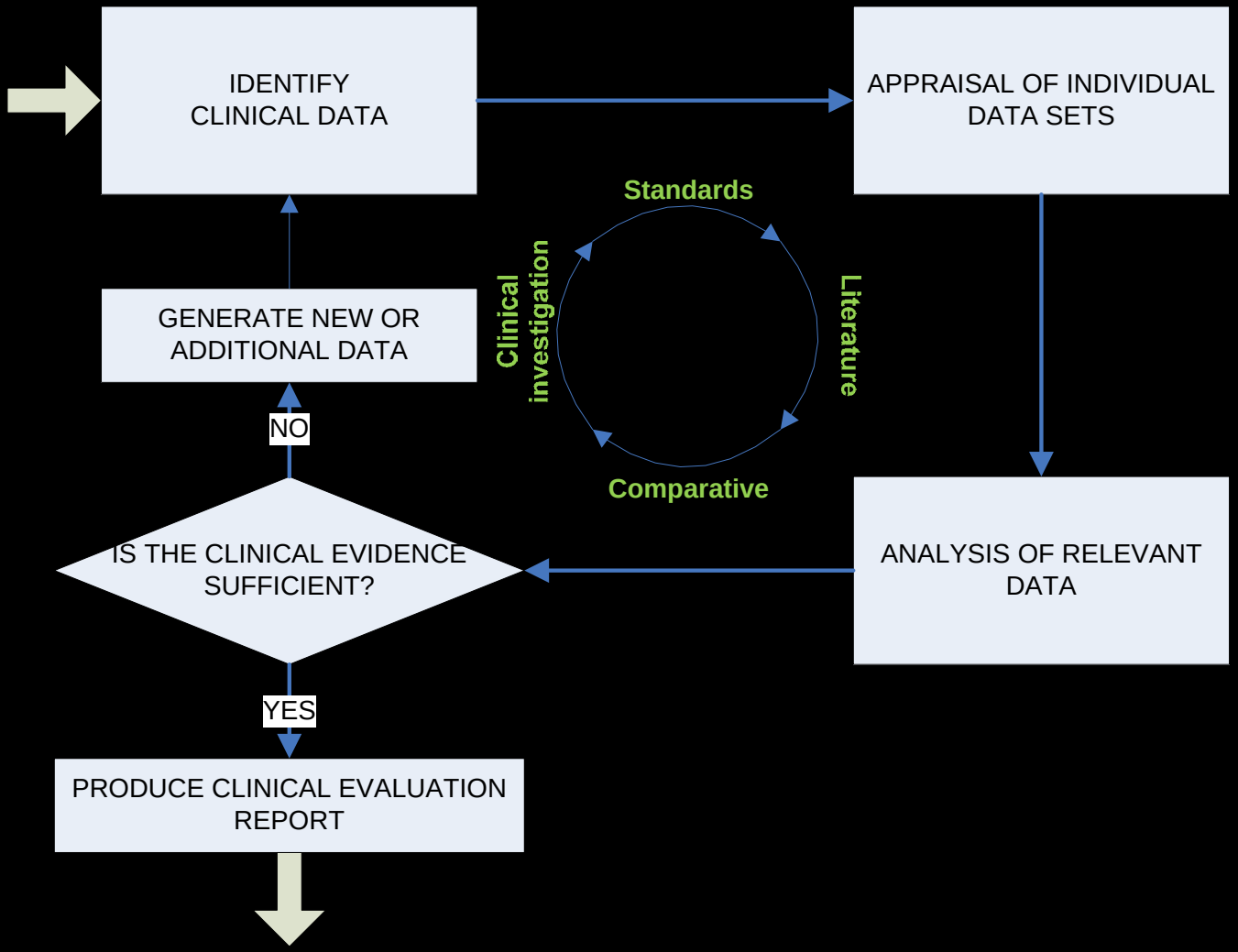
Clinical Evaluation – What Is It?

- 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



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

SG5 – N3 – Clinical Investigations Document

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 & ISO 14155

- SG5 N3 provides preliminary stage guidance on determining the need for an investigation and general considerations
- ISO 14155 provides details of the technical aspects of conducting an investigation
  - While there are points of intersection (e.g. early sections of ISO 14155 Clause 4), the two documents do not generally overlap

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

SG5 – N4 – Post-Market Clinical Follow-Up Document

PMCF

- N4 document currently out for public comment
- A brief overview:

PMCF - Indications

- When is a PMCF indicated?
  - Determined through identification of residual risks that may impact benefit/risk ratio
  - Several examples provided
  - Tend towards not being necessary in cases where medium/long-term safety and clinical performance known from previous use or where other PMS activities would provide sufficient data

PMCF – Elements of a PMCF Study

- Clearly stated objectives
- Scientifically sound design
  - With appropriate rationale and statistical plan
- A study plan (protocol)
- Appropriate implementation
  - Adequate control measures
  - Data analysis
  - Final report with conclusions

PMCF – Use of Study Information

- Form part of clinical evidence to support PMS program
- May result in need to reassess whether device complies with Essential Principles
  - May lead to CAPA

Impact Summary for SG5 Documents

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

Impact of SG5 Documents

- N4 document provides guidance surrounding the design and conduct of post-market clinical follow-up studies
  - When a study is required/justified
  - Appropriate design and conduct
  - How the results are integrated into the benefit/risk analysis

Going Forward…

Ongoing Work of 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
- Address lack of harmonization in Adverse Event Reporting within Clinical Investigations
  - In co-operation with SG2

Going Forward

- Continued liaison with ISO TC 194 to examine areas of common interest
- Assess whether there other new topics should be addressed or go into “maintenance mode”

THANKS!

Contact Info:

Greg LeBlanc
Cook (Canada) Inc.
greg.leblanc@cookmedical.com
+1 (905) 640 7110

Study Group 1

Principles of Medical Device Classification

Michael C. Morton
Medtronic, Inc.
USA

Acknowledgements

- Ed Woo, Medtronic, Inc.

GHTF Final Documents

- Principles of Medical Devices Classification
  - Study Group 1
  - GHTF/SG1/N15:2006
  - June 27, 2006
- Principles of Conformity Assessment for Medical Devices
  - Study Group 1
  - GHTF/SG1/N40:2006
  - June 26, 2006

General Principles

- Regulatory control proportional to risk, taking into account of the benefits of the device
- Classify based on risk
  - Patients
  - Users
  - Others
- Harmonized classification system benefits Regulatory Authorities & manufacturers

Recommendations

- Global Classification System
- Four risk classes
- Class determination based on set of rules
- Clear rules for manufacturers to self identify
- Accommodate technological developments
- Manufacturers should document justification for product classification decision
- Deviation should be weighted against disadvantages of disharmonized international classification

Influencing Factors for Classification

- Multiple rules applies – assigned to highest class
- Multiple medical devices intended to used together
  - Classification rules apply separately to each
- Assemblage of medical devices
  - Intended use different from individual MDs – classified according to new intended use
  - Same intended use – no need to classify as a whole
  - Individual MDs not yet comply w/ regulatory requirements – combination classified as whole according to intended use
- Accessories used together with “parent” MD to achieve intended purpose – same as MD
- Standalone Software
  - Drives or influences the use of separate Medical Device – classified same as device
  - Independent of other Medical Devices – classified separately

GHTF Medical Device Classification System

CLASS	RISK LEVEL	DEVICE EXAMPLES
A	Low Risk	Surgical retractors / tongue depressors
B	Low-moderate Risk	Hypodermic Needles / suction equipment
C	Moderate-high Risk	Lung ventilator / orthopedic implants
D	High Risk	Heart Valve / Implantable defibrillator

Classification Rules

- GHTF/SG1/N15:2006
  - Sec. 8.0 Initial Classification Rules
  - Sec. 8.1 Rational for Additional Rules
  - Appendix A Decision Trees

Case 1 Steroid Eluding Pacing Lead

- **Indications**
  Leads are designed for use with a compatible IPG or an ICD as part of a cardiac system. Leads are intended for delivering therapies and/or sensing in the atrium and/or ventricle of the heart.
- **Steroid-elution technology** reduces inflammation. By eluting a steroid at the lead tip, leads are designed to reduce the typical tissue inflammation.

Case 2 Implantable Constant Flow Infusion System

Indications

- Chronic intrathecal infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain
- Chronic intravascular infusion of floxuridine (FUDR) for the treatment of primary or metastatic cancer

Case 3 Aortic and Mitral Bioprostheses

Indications

- Replacement of impaired native or prosthetic aortic and mitral heart valves.

Case 4 Mechanical Heart Valve

Indications

- This device is indicated in the surgical treatment of cardiac valvular disease when implantation of a prosthetic heart valve is the treatment of choice. It may also be indicated as a replacement for a previously implanted prosthetic heart valve.

Case 5 Heart Valve Sizer

Indications

- **This device is used to measure the size of the natural valve opening to determine the size of the appropriate replacement heart valve.**

Case 6 Anuloplasty System

Indications

- This device is indicated for the reconstruction and/or remodeling of pathological mitral valves. Valvular insufficiency and/or stenosis may be corrected by appropriate repair and annular remodeling.

Study Group 1

Classification of In vitro Diagnostic Devices (IVDs)

Maria Carballo
Therapeutic Products Directorate
Medical Devices Bureau
Health Canada
Canada

Definition of an In-Vitro-Diagnostic 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

Definition (cont'd)

- **Reagent:** chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as IVD Medical Devices
- **Instrument:** equipment or apparatus intended by the manufacturer to be used as IVD Medical Device

Note : International reference materials (e.g. WHO) and materials used for external quality assessment schemes are excluded

CLASSIFICATION

- IVDs are classified differently in worldwide regulations: Medical Devices or Drugs
- GHTF classifies them as Medical Devices, but admits the different nature and risk of IVDs
- Several GHTF documents for medical devices will include guidelines for IVDs (e.g. Essential Principples of Safety & Performance of Medical devices SG1-N41R9:2005), but others will reflect and describe IVDs separately (e.g. Principles of IVD Medical Devices Classification N045:2008; Principles of conformity assessment for IVDs – SG1-N46:2008; the STED for IVDs to come)

PURPOSE OF CLASSIFICATION GUIDANCE

- To assist manufacturers to allocate its IVD Medical Device to an appropriate risk class using a set of harmonized classification principles;
- To base such classification principles on an IVD Medical Device's intended use ; and
- To allow Regulatory Authorities to rule upon matters of interpretation for a particular IVD Medical Device, when appropriate

Criteria for Classification

- Intended use and indications for use as specified by the manufacturer (specific disorder, condition or risk factor for which the test is intended)

- Technical/scientific/medical expertise of the intended user (lay person or professional)

CRITERIA (cont'd)

- Importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician

- Impact of the result (true or false) to the individual and/or to public health

GHTF RISK CLASSES

- Four risk classes, designated from the lowest risk – Class A to the highest risk – Class D

Note: Regulatory requirements increase with the device risk class (refer to the GHTF document entitled Principles of Conformity Assessment for In vitro Diagnostic (IVD) medical devices – SG1-N46:2008)

How to determine the Class of the IVD medical device

1. Determine if the device fits the definition of an IVD medical device
2. Consider all the criteria, rationale and the classification rules to establish the appropriate class
3. If the device has more that one intended use or application resulting in possible multiple classes, the higher class applies
4. If more than one classification rule can be applied, the highest class should be designated

INTENT OF THE CLASSIFICATION CLASSES

CLASS D

- High Individual Risk and High Public Health Risk
- Devices intended to ensure the safety of blood/blood components for transfusion and/or cells, tissues and organs for transplantation
- Devices intended to detect the presence, or exposure to, a transmissible agent that causes a life-threatening, often incurable disease with a high risk of propagation

CLASS C

- High Individual Risk and/or Moderate Public health risk
- Moderate public health risk to the community in general, or in some cases to a more confined environment such as a hospital

CLASS C (cont'd)

- High individual risk :
  - where an erroneous result would put the patient in an imminent life-threatening situation, or
  - have a major impact on the outcome as they are critical or even the sole determinant for correct diagnosis, or
  - stress and anxiety resulting form the information or nature of possible follow up measures

CLASS C (cont'd)

- Devices intended for self-testing, except for those for which the result is not determining a medically critical status, or is preliminary and requires follow up with a laboratory test

CLASS B

- Moderate Individual Risk and/or Low Public Health Risk
- Moderate individual risk:
  - not likely that an erroneous result will lead to death or severe disability, have a major negative impact on patient outcome, place the patient in immediate danger
  - results are usually one of several determinants

CLASS B (cont'd)

- Low public health risk since these devices detect infectious agents that are not easily propagated in the population

CLASS A

- Low Individual Risk and/or Low Public Health Risk
- Devices that present low, minimal risk

Case Study: Classification
CASE 1

HIV Test for screening blood donors or for diagnostic purposes

A false negative result in a blood bank may result in *high public health risk* due to HIV transmission via blood products

GHTF Class D

CASE 2

Test kit for quantitive determination of ferritin in human serum and plasma

Assay used in combination with : symptoms of anaemia, low hemoglobin levels or mean corpuscular volume (MCV)

Low individual risk, no public health risk

GHTF Class B

CASE 3

Assay intended for self-testing determination of glucose levels in the blood

Self-testing/near patient, *high individual risk*, erroneous result places patient in an imminent life-threatening situation

GHTF Class C

QUESTIONS?

QUIZ – Classification of IVDs

CASE 1

ORTHO *T. cruzi* ELISA Test System is an enzyme-linked immunosorbent assay for the qualitative detection of antibodies to *Trypanosoma cruzi (T.cruzi)* in human serum and plasma specimens. This product is intended for use as a donor screening test to detect antibodies to *T. cruzi* in plasma and serum samples from individual human donors, including donors of whole blood, blood components or source plasma, and other living donors. It is also intended for use to screen organ and tissue donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on specimens from cadaveric (non-heart beating) donors. This test is not intended for use on samples of cord blood.
The ORTHO *T. cruzi* ELISA Test System is intended for use in a fully manual mode, in semi-automated mode using the Ortho Summit™ Sample Handling System (Summit) or in automated mode with the Ortho Summit™ System (OSS).
This assay is not intended for use as an aid in diagnosis

CASE 1 - response

- *Class D by Rule 1*
- Device intended as a donor screening test to detect antibodies to *T. Cruzi*, the causative agent of Chagas disease (a chronic, asymptomatic, untreatable, and potentially fatal disease). High public and individual health risk.

CASE 2

The IMx Sirolimus assay is an in vitro reagent system for the quantitative determination of sirolimus in human whole blood as an aid in the management of patients receiving sirolimus therapy.

CASE 2 - Response

- *Class C by Rule 3*
- Sirolimus is an immunosuppressive drug for renal transplant immunosuppressive therapy. Because of potential toxic effects associated with high trough levels of sirolimus, therapeutic drug monitoring of sirolimus immunosuppressive therapy is recommended.
- Device is intended to monitor level of medicine where there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation to the patient. High individual risk

CASE 3

The BD ProbeTec GC Q Amplified DNA Assay, when tested with the BD Viper System in Extracted mode, uses Strand Displacement Amplification technology for the direct, qualitative detection of *Neisseria gonorrhoeae* DNA in clinician-collected female endocervical and male urethral swab specimens, patient collected vaginal swab specimens (in a clinical setting), and male and female urine specimens. The assay is indicated for use in asymptomatic and symptomatic female individuals and symptomatic male individuals to aid in the diagnosis of gonococcal urogenital disease.

CASE 3 - Response

- *Class C by Rule 3*
- Device intended to determine the presence of, or exposure to, a sexually transmitted agent that causes a serious disease and there is a risk of propagation in the population

CASE 4

Immulite 2000 PSA

For in vitro diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of prostate-specific antigen (PSA) in human serum, as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older. This assay is further indicated as an adjunctive test to aid in the management of prostate cancer patients.

CASE 4 - Response

- *Class C by Rule 3*
- Device is intended to aid in the detection of prostate cancer. It is also intended to aid in the management/monitoring of prostate cancer patients following surgical or medical treatment. Since there are two intended uses: cancer detection (Class C) and monitoring (Class B by rule 6), the highest classification applies. High individual risk.

CASE 5

BBL™ Columbia Agar with 5% Sheep Blood

Columbia Agar with 5% Sheep Blood is a highly nutritious general purpose medium for the isolation and cultivation of nonfastidious and fastidious microorganisms from a variety of clinical and nonclinical material.

CASE 5 - Response

- *Class A by Rule 5*
- The device represents a minimal risk.

CASE 6

PTS PANELS and CardioChek Test Strips are intended to be used with the CardioCheck brand analyzers by medical professionals and individuals in the home to measure cholesterol, high and low density lipoprotein cholesterol, triglycerides, glucose and ketones in whole blood. Cholesterol measurements are used in the diagnosis and treatment of disorders involving excess cholesterol in the blood and lipid and lipoprotein metabolism disorders. Lipoprotein measurements are used in the diagnosis and treatment of lipid disorders (such as diabetes mellitus), atherosclerosis, and various liver and renal diseases. Glucose measurements are used in the management of carbohydrate metabolism disorders. Ketones measurements are used in the diagnosis and treatment of acidosis (a condition characterized by abnormally high acidity of body fluids) or ketosis (a condition characterized by increased production of ketone bodies) and for monitoring patients on ketogenic diets and patients with diabetes.

CASE 6 - Response

- *Class C by rule 4*

- Device is intended for blood glucose determinations for near patient testing. Even though the other analytes may fall into a lower class, the highest classification applies.

CASE 7

The Cepheid® Xpert MRSA Assay performed on the GeneXpert® Dx System (Xpert MRSA) is a qualitative *in vitro* diagnostic test designed for rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA) from nasal swabs in patients at risk for nasal colonization. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA DNA. The Xpert MRSA Assay is intended to aid in the prevention and control of MRSA infections in healthcare settings. The Xpert MRSA Assay is not intended to diagnose MRSA nor to guide or monitor treatment for MRSA infections. Concomitant cultures are necessary only to recover organisms for epidemiological typing or for further susceptibility testing.

CASE 7 - Response

- *Class C by Rule 3*
- Device is intended for the rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA), a transmissible agent responsible for nosocomial infections. False positive results would trigger antibiotics being prescribed unnecessarily, false negative results could mean that antibiotics may not be prescribed.
- Moderate individual and high public risk.

CASE 8

Dimension Vista® Vitamin B12 Flex® reagent cartridge (B12)

The B12 Flex® reagent cartridge is an in vitro diagnostic test for the quantitative measurement of Vitamin B12 in human serum and plasma on the Dimension Vista® system. Measurements obtained by this device are used in the diagnosis and treatment of anemias of gastrointestinal malabsorption.

Dimension Vista® Folate Flex® reagent cartridge (FOL)

The FOL Flex® reagent cartridge is an in vitro diagnostic test for the quantitative measurement of folate in human serum and plasma on the Dimension Vista® system. Measurements obtained by this device are used in the diagnosis and treatment of megaloblastic anemia.

CASE 8 - Response

- *Class B by Rule 6*

- Moderate individual risk. An erroneous result is not likely to put the patient in immediate danger or have a significant negative impact on long-term outcome. It is not the sole determinant.

5th APEC Seminar – May 2009

Study Group 1

INTRODUCTION TO

SUMMARY TECHNICAL DOCUMENTATION

(STED)

Brenda Murphy
MEDEC/SciCan Ltd.
Canada

STED – What is it?

- A summary document that is created by the manufacturer from the full existing technical documentation concerning the design, development & manufacturing of his device
- This subset contains documentary evidence that would be considered sufficient for a regulatory agency to confirm conformity of the medical device to the essential principles
- The STED reflects the status of the device at the time of submission

STED – Why was it developed?

- Today, pre-market submission content & formats vary widely from country to country
- Manufacturers must select a variety of data to present in a country-specific manner
- This approach can be time consuming & confusing for both the manufacturer and the regulator

STED – Development by GHTF SG.1

- STED format originally intended as a “harmonized submission format” for use by GHTF member countries
- If successful, the STED could then be adopted for use by other regions
- Concept of the STED approach was first introduced by GHTF SG1. members under a pilot program beginning in 2001 with several time extensions permitted since that date

STED – beyond ....

- a new revision of the STED document was initiated & completed in 2007 to include all member countries of SG1.
- this latest revision includes more descriptive information about content & amount of data expected to be included in the document
- the final STED guidance doc. was released in May 2008 – available on the GHTF web-site
- Applies to all medical devices but excludes *In Vitro diagnostics*

STED – What does it contain?

- STED format (a revisit):
  1. Device description – general descriptive information
     - product specifications
     - reference to previous generations
     - reference to similar cleared devices (predicates)
  2. Labeling – all labels, instructions, brochures in a language acceptable to the RA/CAB
  3. Design & manufacturing information
     - Sufficient to allow the reviewer to obtain a general understanding of the design stages and the manufacturing processes
     - Identity of the sites where each of the activities are performed together with any applicable QMS certificates

STED – What does it contain?

4. Essential principles of safety & performance checklist
   - Used to better understand how the manufacturer demonstrates conformity to the essential principles for his device
   - May reference specific standards, test reports, study reports, validation documents
   - Contains references to any actual controlled documents
   - Sample table contained within the STED guidance doc.
5. Risk analysis & control summary
   - Should be based on recognized standards

STED – What does it contain?

6. Product verification & validation
   - level of detail will vary depending upon the Class & complexity of the device
   - summarizes results of verification & validation studies to demonstrate conformity with Essential Principles
   - Biocompatibility information
   - Biological safety of all materials used in the device
   - information of sterilization validation, if applicable
   - info. on software design, development & validation
   - detailed info. on animal studies, if applicable
   - Clinical evidence to demonstrate conformity

STED – What does it contain?

7. Declaration of Conformity
   - not an actual part of the STED but may be annexed to it
   - content of the Declaration of Conformity is described in the GHTF document GHTF/SG1/N40:2006– *Principles of Conformity Assessment for Medical Devices*

STED – How much detail?

- The depth & detail is dependent upon the class & complexity of the device
- Also depends if the device:
  - is new to the manufacturer
  - is already marketed but now carries a new indication for use
  - involves new technology or novel or hazardous materials
  - is associated with a large number of adverse events
  - raises specific public health concerns

STED – When is it used?

- Premarket:
  - STED for Class C & D devices to be prepared and submitted to regulatory authority
  - STED for Class A & B devices prepared and submitted only upon request of the RA/CAB
  - Manufacturer should always retain a copy of any STED submitted for future reference

STED – When is it used?

- Post market:
  - Submitted upon request of an RA/CAB:
    - to demonstrate continued conformity of a Class C or D device
    - to investigate conformity of a Class A or B medical device

    BUT

    - the STED is not usually used to assist in any post market investigation of adverse events

STED – Potential benefits

- Goal of STED: (**regulators** perspective)
  - to provide improved access to new technologies
  - to reduce the burden on the regulators by promoting a review of documents presented in a consistent manner
  - to provide direction to those markets developing device regulations for the first time

STED – Potential benefits

- Goal of STED: (**manufacturers** perspective)
  - to reduce the burden on manufacturers of conflicting pre-market submission formats & unique content
  - to permit the creation of one core dossier for all submissions
  - to minimize regulatory barriers
  - to facilitate trade

STED – Pilot perspective

- The STED pilot program **objectives** included:
  - Evaluation over the period of the pilot by industry and regulators of the proposed GHTF format & content
  - Evaluation as to any reduction of the regulatory burden on manufacturers
  - Confirmation of general awareness of the STED guidance

STED – Pilot experience

- What did we find ?

> further discussion from a Canadian perspective.

Study Group 1

STED IMPLEMENTATION

The Canadian Experience

Maria Carballo
Therapeutic Products Directorate
Medical Devices Bureau
Health Canada
Canada

TOPICS TO BE COVERED

- **STEPS TO IMPLEMENTATION**
  - IMPLEMENTATION OF A PILOT PROJECT
  - CHALLENGES
  - EXPERIENCE GAINED FROM THE PILOT PROJECT
  - FULL IMPLEMENTATION PLAN
- **REGULATOR EXPECTATIONS FROM THE STED**

STEPS TO IMPLEMENTATION

IMPLEMENTATION OF A PILOT PROJECT

Objective:

- To evaluate the STED format and content requirements
- To reduce regulatory burden on manufacturers

PARTICIPANTS OF THE PILOT PROGRAM

- GHTF Founding members
  - Australia, Canada, EU, Japan, USA

- Industry

SCOPE OF THE PILOT PROGRAM

- Class C and D medical devices
- Manufacturers encouraged to prepare and submit STEDs for the same devices to as many of the GHTF member countries as possible.

CANDIDATE DEVICES FOR THE PILOT

- Intravascular Catheters
- External Infusion Pumps
- Endosseus Dental Implants
- Hemodialyzers and Hemodialysis Catheters
- Plasma Cell Separators for Therapeutic Use
- X-Ray Bone Densitometers
- Fluoroscopic X-Ray
- Urological Catheters
- ECG Monitors

CANDIDATE DEVICES FOR THE PILOT (Cont'd)

- Computed Tomography Scanners
- Magnetic Resonance Imaging Devices
- PTCA Catheters
- Coronary Stents
- Implantable pacemakers
- Implantable Cardioverter Defibrillators
- Orthopedic Implants

DURATION OF THE PILOT

- Originally 1 year (2003 – 2004)
- Indefinitely extended until fully implemented

Implementation Tasks

- **Notification to Industry**
- **Complementary Documents to develop:**
  - Guidance Document
  - Fact Sheet
- **Website Posting**

NOTIFICATION TO INDUSTRY

- Posted on TPD website with links to the Guidance Document and the Fact Sheet

GUIDANCE DOCUMENT

- Explained the Pilot Program
- Procedures to follow
- Comparison between requirements of the Canadian Medical Devices Regulations and the STED document for both Class C and D devices, highlighting the differences
- Links to all relevant documents

FACT SHEET

- What is GHTF?
- What is the STED?
- What is the STED Pilot Program about?
- Who will be participating in the STED Pilot?
- What applications are eligible?
- Why should manufacturers participate?
- What are the next steps?
- How long will the STED Pilot run?
- What are the anticipated outcomes of the Pilot?
- Where to obtain more information on GHTF and the STED Pilot Program?

CHALLENGES

- Introduction of a new format and concept to reviewers
- Lack of response by manufacturers
- n = 15 to 20 (Mostly Class D Cardiovascular devices)

EXPERIENCE GAINED FROM THE PILOT

- All applications met the STED and the “extra” Canadian requirements
- Overall positive comments from the reviewers

COMMENTS/FINDINGS FROM REVIEWERS

- STED user friendly, did not inhibit review process
- Additional time needed for reviewer to understand what the STED was and to review the applicable documents
- Essential Principles checklist useful and complete
- Good use of Table of contents, Executive Summaries and general summaries

EVALUATION FROM DIFFERENT REGIONS

- An analysis of the pilot program was never done as some of the regions like Europe never received any STEDs.

STED FULL IMPLEMENTATION PLAN

- Considerations:
  - STED implementation both TPD and GHTF wide effort
  - Effective consultation/collaboration with industry essential
  - Despite reality of “regional STEDs”, Health Canada is committed to not duplicating information already in the STED

FULL IMPLEMENTATION PLAN

Legislative Changes?

Not required in order to implement the STED

FULL IMPLEMENTATION PLAN

- Using the STED, the MDB would need to established a prescribed format in guidance for the premarket information for Class C and D licence applications
- Currently a standard format is not used by all manufacturers
- Need to address requirements that are in the Canadian Regulations but not in the STED

IMPLEMENTATION TASKS

- Short Term

  - Publish a Notice of Intent to Adopt the use of the STED in premarket applications for Class III and IV (i.e., Class C and D) medical devices

    (First quarter 2009)

IMPLEMENTATION TASKS

- Short Term
  - Draft a new Guidance document entitled “Guidance for Manufacturers preparing a Premarket Application using the Summary Technical Documentation (STED)” that will replace the current document “Guidance for manufacturers preparing a Premarket Application using the Summary Technical Documentation (STED) for demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices”
  - The Guidance document will allow for voluntary filling of STED-based premarket applications for Class III and IV medical devices

    (January – July 2009)

IMPLEMENTATION TASKS

- Readiness for Health Canada to strongly encourage the use of the STED in premarket applications
- eSTED/eReview
- Continuing Guidance Development
- Revise internal Review templates and corresponding Review SOPs

REGULATORY EXPECTATIONS FROM THE STED

- The STED should demonstrate conformity to the Essential Principles of Safety and Performance and the Canadian Regulatory requirements
- The information provided should be sufficient for a regulatory agency to confirm conformity.

REGULATORY EXPECTATIONS (cont'd)

- A compilation of a subset of documents normally generated during the design process
- The number of documents and depth of detail in the STED tends to be proportional to the risk class and complexity of the device
- Some tailoring may be required

REGULATORY EXPECTATIONS (cont'd)

- Evidence of conformity provided in tabular form with cross-reference to supporting documentation
- Executive Summary
- Results and conclusions of studies

REGULATORY EXPECTATIONS (cont'd)

- Depth of detail depends on:
  - Device Classification
  - Complexity of the device
  - Novel technology
  - Extension of intended use from an already marketed device
  - Association with significant number of adverse events, user errors
  - New or potential hazardous materials
  - Public Health concerns

REGULATORY EXPECTATIONS (cont'd)

- KEY MESSAGE:

  - The documents submitted must provide all relevant information in such a way that it allows the reviewer to understand the subject and the manufacturer's conclusions

REGULATORY EXPECTATIONS (cont'd)

- Requirements to meet Canadian Regulations:
  - ISO 13485 Certificate
  - Quality Plan (Class D)
  - Marketing History
  - Labelling (French and English)

QUESTIONS

Proposed Document –

Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer

5th APEC- Funded Seminar on Harmonization of Medical Device Regulation

Dr.Petra Kaars-Wiele
EDMA/ Abbott Laboratories, Germany

GHTF Guidance Document

- Proposed document prepared by SG1
- Available on GHTF website
- Comments to SG1 are welcome

Why do we need the Document?

- The term „manufacturer“ appears in many GHTF documents, but also in many international regulations
- The term is associated with various obligations and responsibilities
- A harmonized definition would benefit authorities and manufacturers to develop a consistent approach how to place products onto the market
- It allows regulatory authorities to establish identity of person who takes responsibility for ensuring the finished medical device (incl. IVDs) meets relevant requirements within ist jurisdiction

Definition: Manufacturer

- "Manufacturer" means any natural or legal person[1] 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).
-

[1] The term "person" that appears here and in the other definitions of this document, includes legal entities such as a corporation, a partnership or an association.

Definition: Authorized Representative

- **“**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 specified tasks with regard to the latter’s obligations under that country or jurisdiction’s legislation.

Definition: Distributor

- “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.

A Distributor is not a Manufacturer

A distributor who indicates its 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 may affect safety, performance or intended use, is not considered a manufacturer.

Definition: Importer

"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.

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.

But….

a single party may fulfill one or more of these roles

e.g. , a manufacturer may not only distribute the products but it may also act as a distributor or importer of devices from a different manufacturer.

QUIZ

Scenario 1

- A Japanese company produces its product from incoming material to the end product under its name. They are responsible for all aspects of the product.

- Who is the Manufacturer?

Scenario 2

- A German company has a contract with a research company in the Netherlands to design a new IVD assay. The design is transfered to a company in Spain. This company produces the assay and the final product is delivered for final distribution into the German company‘s warehouse for further distribution. Country of Origin is Spain. The German company holds responsible for all aspects of the product including supplier control.
- Who is the Manufacturer?

5th APEC Seminar – May 2009
Study Group 1

Proposed Document –

Registration of Manufacturers and other Parties and Listing of Medical Devices

Brenda Murphy
MEDEC/SciCan Ltd.
Canada

Registration & Listing – defined

- *Registration* > a process by which a party submits information to the Regulatory Authority (RA) in a jurisdiction regarding the identification and establishment location(s) of the manufacturer & other parties responsible for supplying a medical device(s) to the market in that jurisdiction (the manufacturer may authorize a representative to fulfill his requirements)

- *Listing* > a process by which a party submits information to the Regulatory Authority (RA) in a jurisdiction regarding the identification of a medical device(s) that is supplied to the market in that jurisdiction

Registration & Listing – the basics!

- registration & listing are considered to be *basic* elements of regulatory control
- most countries with existing medical device regulations have already established registration & listing requirements
- for countries with limited resources or emerging regulations, registration & listing may be the first or only manner of regulatory control

Registration & Listing – Why?

- information collected by the RA assists with possible regulatory actions (e.g. field corrective actions & recalls)
- device purchasers & users such as hospitals & clinics are able to identify the products that are available within their markets, if listings are made public
- they can also identify the location of the manufacturer or distributor of device, if needed

Registration & Listing – Why?

- applies to all types of medical devices, including *in vitro diagnostics*
- to date, this type of information is *not* harmonized
- this document provides common definitions for each term
- clarifies roles & responsibilities of each party
- provides guidance on data content

Registration requirements – Role of RA

- identify which parties are required to register (need is dependent on a variety of factors)
- Specify:
  - the info. required
  - the format required
  - frequency to be provided
  - mechanism in which to provide the information
  - language requirements for the information

Registration requirements – Role of Registrant

- provide required information
- attestation to accuracy
- update previously provided info. within 30 days of changes
- provide ongoing “confirmation of accuracy” upon request by RA (annually?)

Medical Device Listings

- Listings provide info. on devices that have been, or will be, supplied to the market
- Outstanding question as to products no longer offered for sale – register or not?
- Outstanding question as to timing of registration?
- Registrant must also still fully comply with any regulations for the device (i.e. file reviews/submissions) that apply within the jurisdiction

Medical Device Listings – Role of RA

- Identify parties required to register
- Specify information required
- Specify format, mechanism & frequency
- Designate the language
- Assign codes to each listed device
- Provide a searchable, secure database

Medical Device Listings – Role of Registrant

- Provide required information
- Attest to accuracy
- Info. update for changes

  (Outstanding question as to timing of updates either annually or within 30 days)
- provide ongoing “confirmation of accuracy” upon request by RA (annually?)

Registration & Listing - SG1(WD)/N065

- Seeks to provide a balance between safeguarding health of citizens & avoiding unnecessary burdens on industry
- Encourage review & comments to this document to effectively set that balance
- Document currently available on the GHTF website at www.ghtf.org as an SG1. proposed document
- Comments due by Sept. 2, 2009

GHTF SG2 Guidance:

Reporting of Medical Device Adverse Events

Dr Ekkehard Stösslein – BfARM
Dr Philippe Auclair - Abbott Vascular– EUCOMED

Post-Market Surveillance

- Post-Market Surveillance is the collection of information on the quality, safety or performance of Medical Devices after they have been placed in the market.
- A balanced Post-Market Surveillance system will contain an appropriate mix of proactive and reactive activities.

Post-Market Vigilance

- (Post-Market) Vigilance is the reporting and investigation of medical device adverse events and incidents. Both the manufacturer and the Regulatory Authority play major roles.

- By its very nature, Vigilance is a REACTIVE activity *(the manufacturer or authority receive reports and REACT to them)* - this is not intended to be a derogatory statement

A Pictorial view of PMS

Post-Market Surveillance Information is used for:

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

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?

SG2 Guidance

Report Handling & NCAR Program

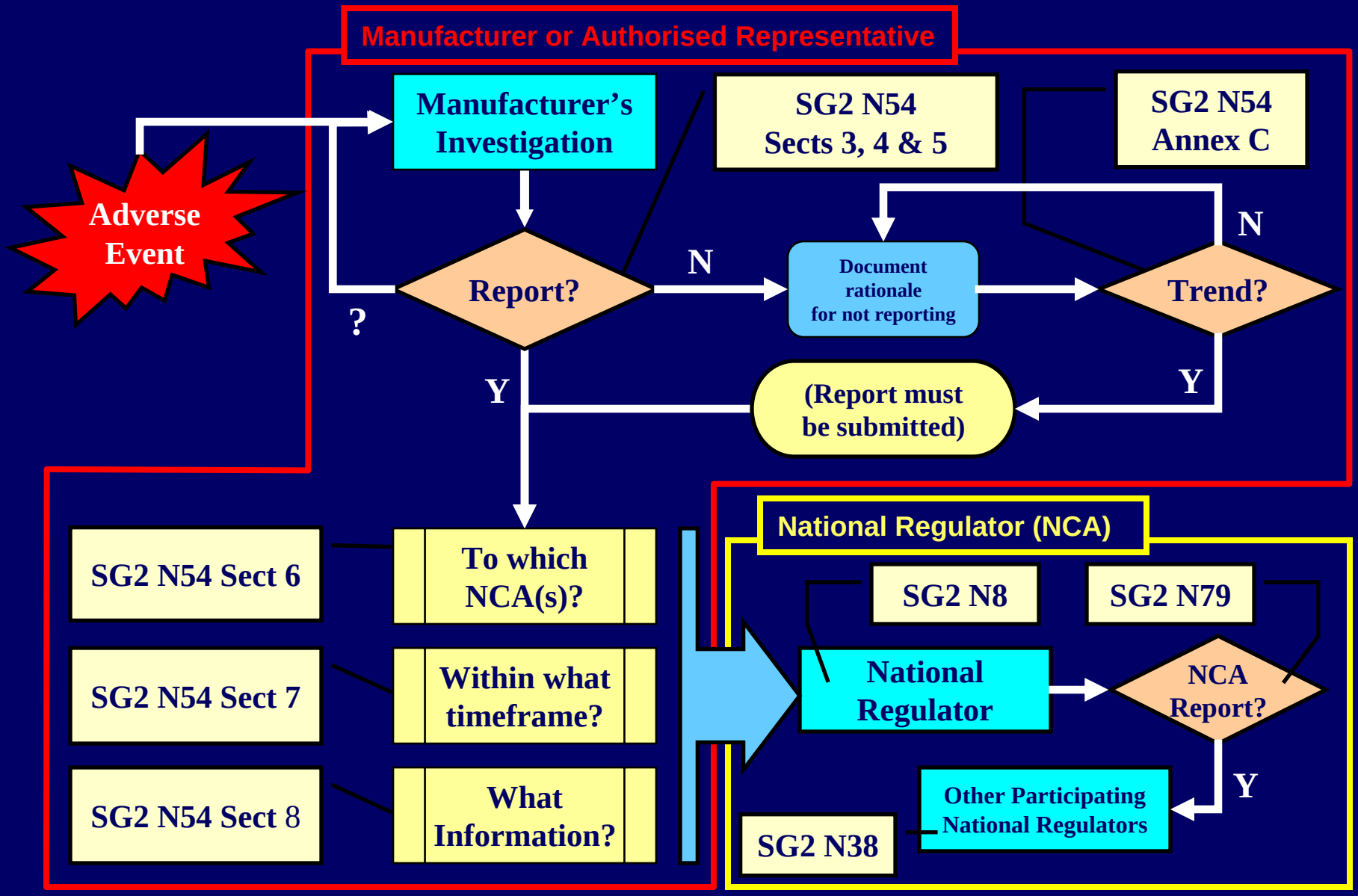
- SG2-N8R4: Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices
- SG2-N9R11: Global Medical Device Competent Authority Report
- SG2-N20R10: National Competent Authority Report Exchange Criteria
- SG2-N38R14 Application Requirements for Participation in the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

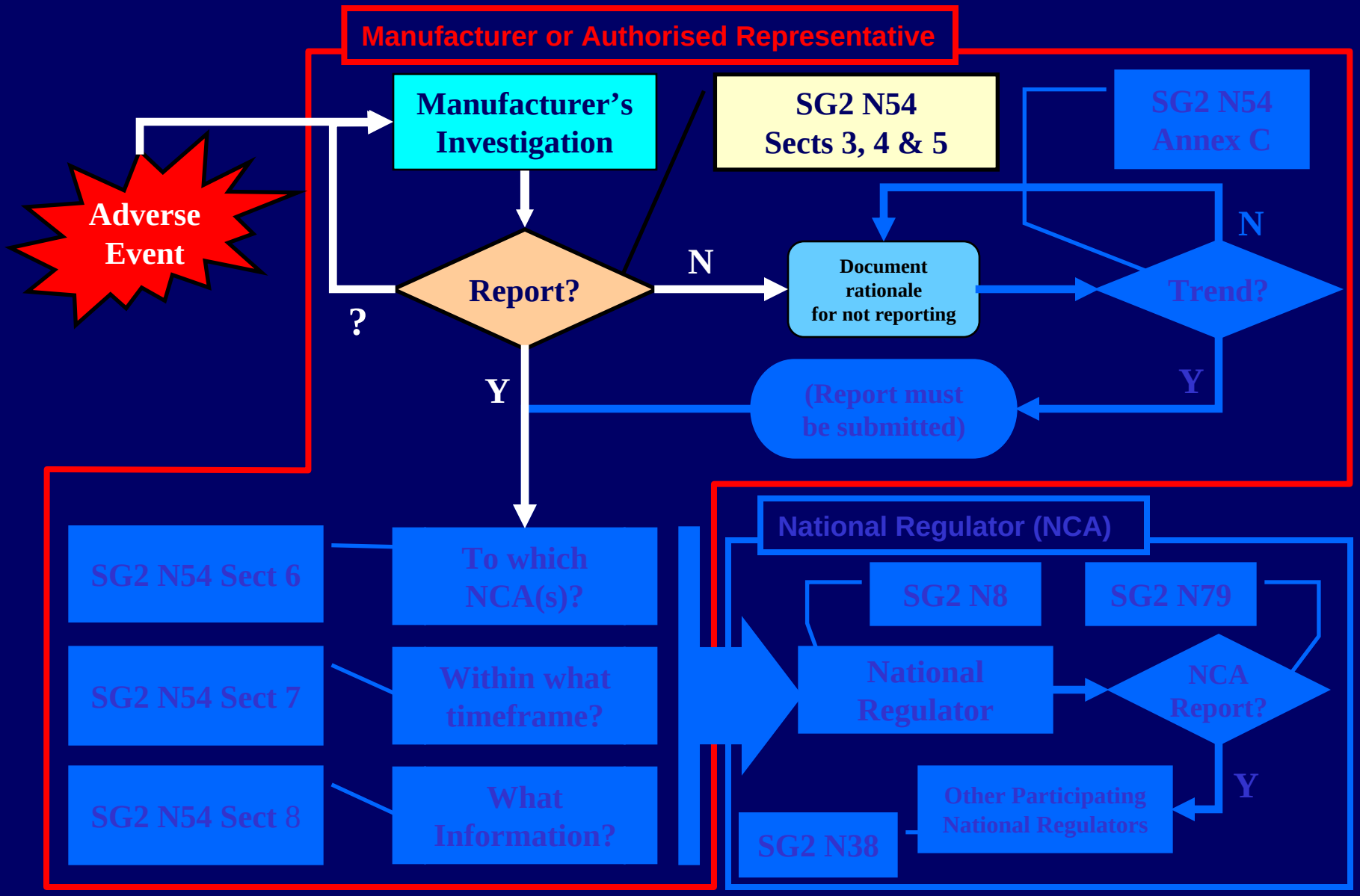
Table of Contents

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

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

EVENT

- Malfunction or deterioration
- Inadequate design or manufacture
- Inaccuracy in labeling
- Significant public health concern
- Other information from testing or literature
- A change in trend

ASSOCIATION (WITH THE DEVICE)

- When the association with the device is difficult to establish, the manufacturer must rely on:
  - Opinion from healthcare professional
  - Previous similar events
  - Other information available to the manufacturer
- If there is any doubt, assume that the device was associated with the event.

SERIOUS INJURY

- Life threatening illness or injury
- Permanent (irreversible) impairment of a body function or permanent damage to a body structure
- A condition requiring medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

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 Rule 1

1) Deficiency of a new device found by the user prior to its use

   Deficiencies of devices that would always be detected by the user and where no serious injury has occurred, do not need to be reported

Exemption Rule 1 Example

1) Deficiency of a new device found by the user prior to its use

   Example-

   User performs an inflation test prior to inserting the balloon catheter in the patient as required in the instructions for use accompanying the device. Malfunction on inflation is identified. Another balloon is used. Patient is not injured

Exemption Rule 2

2) Adverse event caused by patient conditions

When the manufacturer has information that the root cause of the adverse event is due to a patients condition, the event does not need to be reported. These conditions could be preexisting or occurring during device use

Exemption Rule 2 Example

2) Adverse event caused by patient conditions

Example-
Revision of an orthopedic implant due to loosening caused by the patient developing osteoporosis

Exemption Rule 3

3) Service life or shelf life of the medical device

When the only cause for the adverse event was that the device was used beyond its service life as specified by the manufacturer and the failure mode is not unusual, the adverse event does not need to be reported

Exemption Rule 3 Example

3) Service life of the medical device

Example-

Loss of sensing after a pacemaker has reached end of life. Elective replacement indicator has shown up in due time according to device specification. Surgical explantation of pacemaker required

Exemption Rule 4

4) Malfunction protection operated correctly

Adverse events which did not lead to serious injury or death, because a design feature protected against a malfunction becoming a hazard, do not need to be reported

Exemption Rule 4 Example

4) Malfunction protection operated correctly

Example-

After a malfunction of an infusion pump it gives an appropriate alarm and stops (in compliance with relevant standards). There was no injury to the patient

Exemption Rule 5

5) Negligible likelihood of occurrence of death or serious injury

Adverse events which could lead, but have not yet led, to death or serious injury, but have a remote likelihood of causing death or serious injury, and which have been established and documented as acceptable after risk assessment do not need to be reported

Exemption Rule 5 Example

5) Negligible likelihood of occurrence of death or serious injury

Example-

Manufacturer of pacemaker released on the market identified a software bug and determined that the likelihood of occurrence of a serious injury with a particular setting is negligible. No patients experienced adverse health effects

Exemption Rule 6

6) Expected and foreseeable side effects which meet all the following criteria :

- Clearly identify in the manufacturers labeling
- Clinically well known and having a certain qualitative and quantitative predictability when used & performed as intended
- Documented in the device master record, with risk assessment prior to occurrence
- Clinically acceptable in terms of patient benefit are not reportable

Exemption Rule 6 Example

6) Expected and foreseeable side effects

Example-

Placement of central line catheter results in anxiety reaction and shortness of breath. Both reactions are known and labeled side effects

Exemption Rule 7

7) Adverse events described in an advisory notice

AEs that occur after a manufacturer has issued an advisory notice need not be reported individually if specified in the notice. Advisory notices include removals from the market, corrective actions, and product recalls. The manufacturer should provide a summary report, the content and frequency of which should be agreed with the relevant NCA

Exemption Rule 7 Example

7) Adverse events described in an advisory notice

Example-

Manufacturer issued an advisory notice and recall of a coronary stent that migrated due to inadequate inflation of an attached balloon mechanism. Subsequent examples of stent migration were summarized in quarterly recall reports and individual events did not have to be reported

Exemption Rule 8

8) Reporting exemptions granted by NCA

Upon request by the manufacturer and agreement by NCA common and well-documented events may be exempted from reporting or changed to periodic summary reporting

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

GHTF N54 Section 5 & Annex D
Use Errors

- Use Error: Section 5 (N54) + appendix D

  Act, or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator

  Examples-
  - Despite proper instruction and proper design according to manufacturers analysis operator presses wrong button
  - Operator enters incorrect sequence and fails to initiate an action such as infusion

GHTF N54 Section 5 & Annex D
Abnormal Use

- Abnormal Use:

  Act, or omission of an act by the operator or user of a medical device as a result of conduct that is beyond any reasonable means of risk control by the manufacturer

  Examples-

  – Use of a medical device in installation prior to completing all initial performance checks as specified by the manufacturer

  – Continued use of a medical device beyond the manufacturers defined planned maintenance interval as a result of user's failure to arrange for maintenance

Use Errors & Abnormal Use

Note - Foreseeable misuse that is warned against in the instructions for use is considered abnormal use if all other reasonable means of risk control have been exhausted

Use Error - Reportability

- Use errors related to medical devices, which did result in death or serious injury or serious public health threat should be reported by the manufacturer to the National Competent Authority

Use Error - Reportability

- Use errors related to medical devices which did not result in death or serious injury or serious public health concerns, need not be reported by the manufacturer to the national competent authorities.
- Use errors become reportable by the manufacturer to the national competent authorities when a manufacturer:
  - Notes a change in trend that can potentially lead to death or serious injury of public health concern.
  - Initiates corrective action to prevent death or serious injury or serious public health concern.

Abnormal Use - Reportability

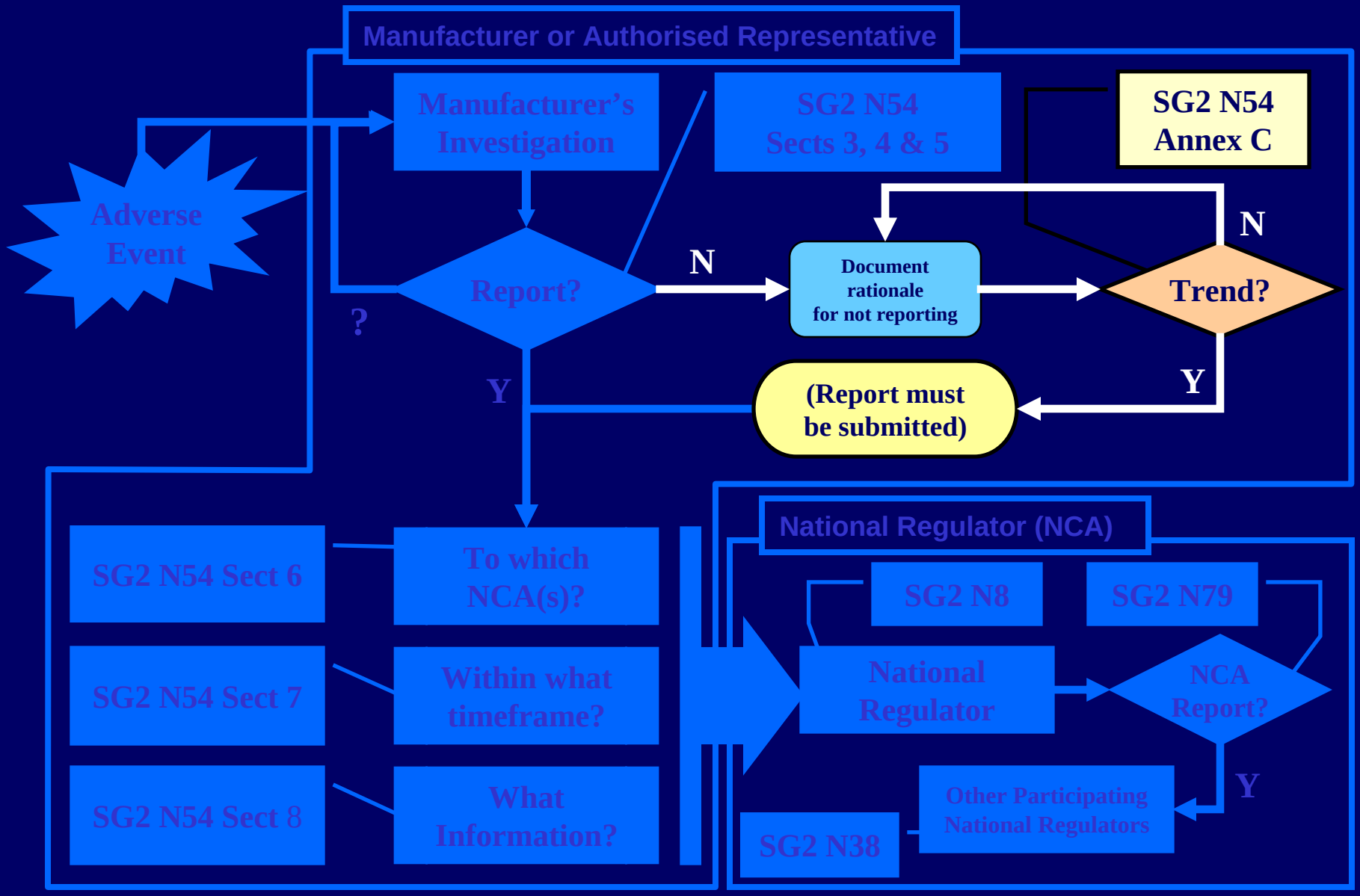
- Abnormal use need not to be reported by the manufacturer to the national competent authority under adverse event reporting procedure. Abnormal use should be handled by the healthcare facility and appropriate regulatory authorities
- If manufacturers become aware of instances of abnormal use, they may bring this to the attention or other appropriate organizations and healthcare facility personnel

The Universe of Device Associated Adverse Events

R=Report
NR*= No Report*

= Death
= Serious Injury
= Malfunction /No Incident

Trends

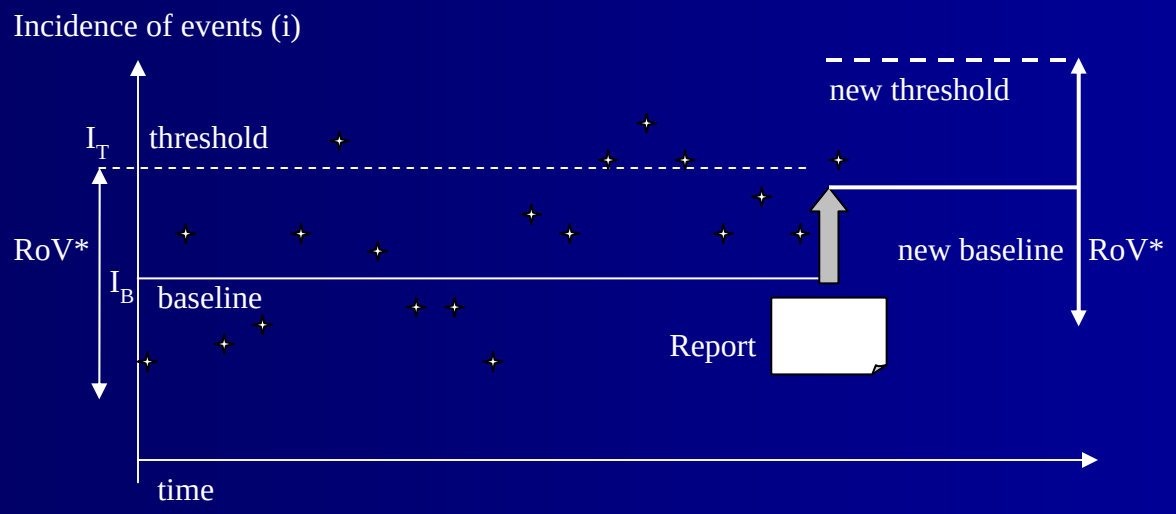

Manufacturer or Authorised Representative
Manufacturer's Investigation
SG2 N54 Sects 3, 4 & 5
SG2 N54 Annex C
Adverse Event
Report?
N
Document rationale for not reporting
Trend?
N
Y
(Report must be submitted)
?
Y
SG2 N54 Sect 6
To which NCA(s)?
SG2 N54 Sect 7
Within what timeframe?
SG2 N54 Sect 8
What 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

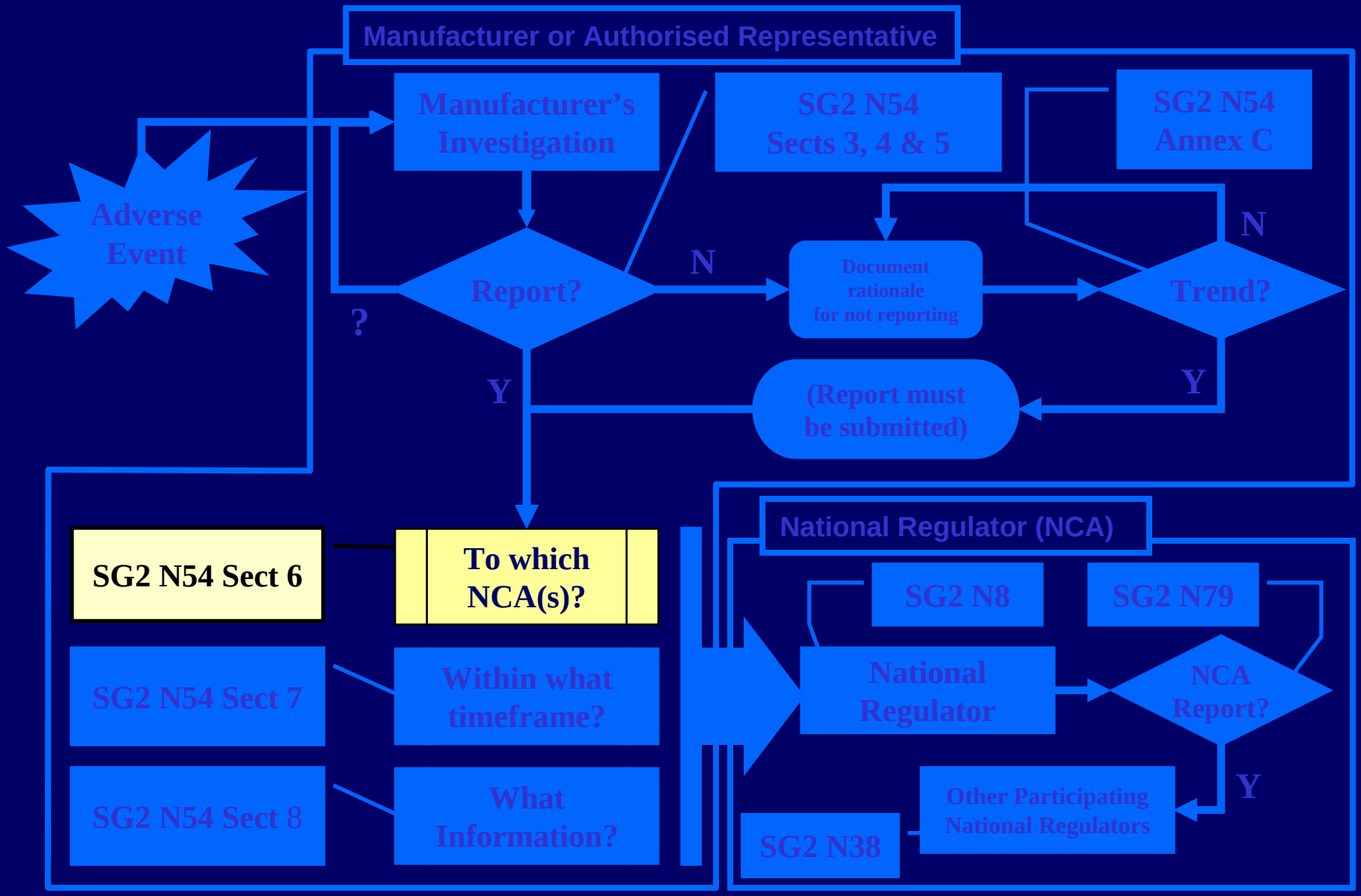
AE Trend Reporting

- Example of an upward shift in trend



* normal Range of Variance

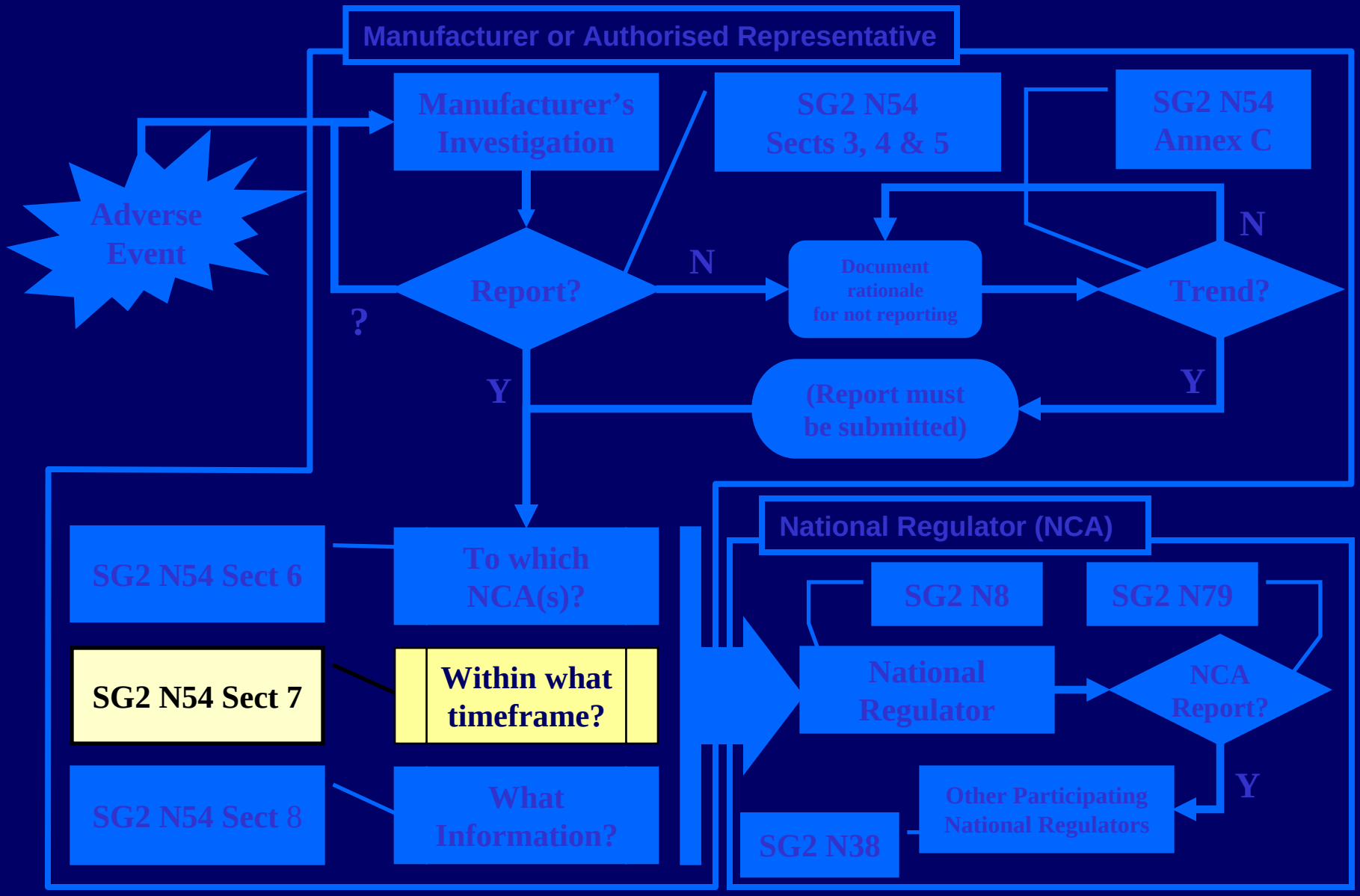
To Which NCAs to Report?



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

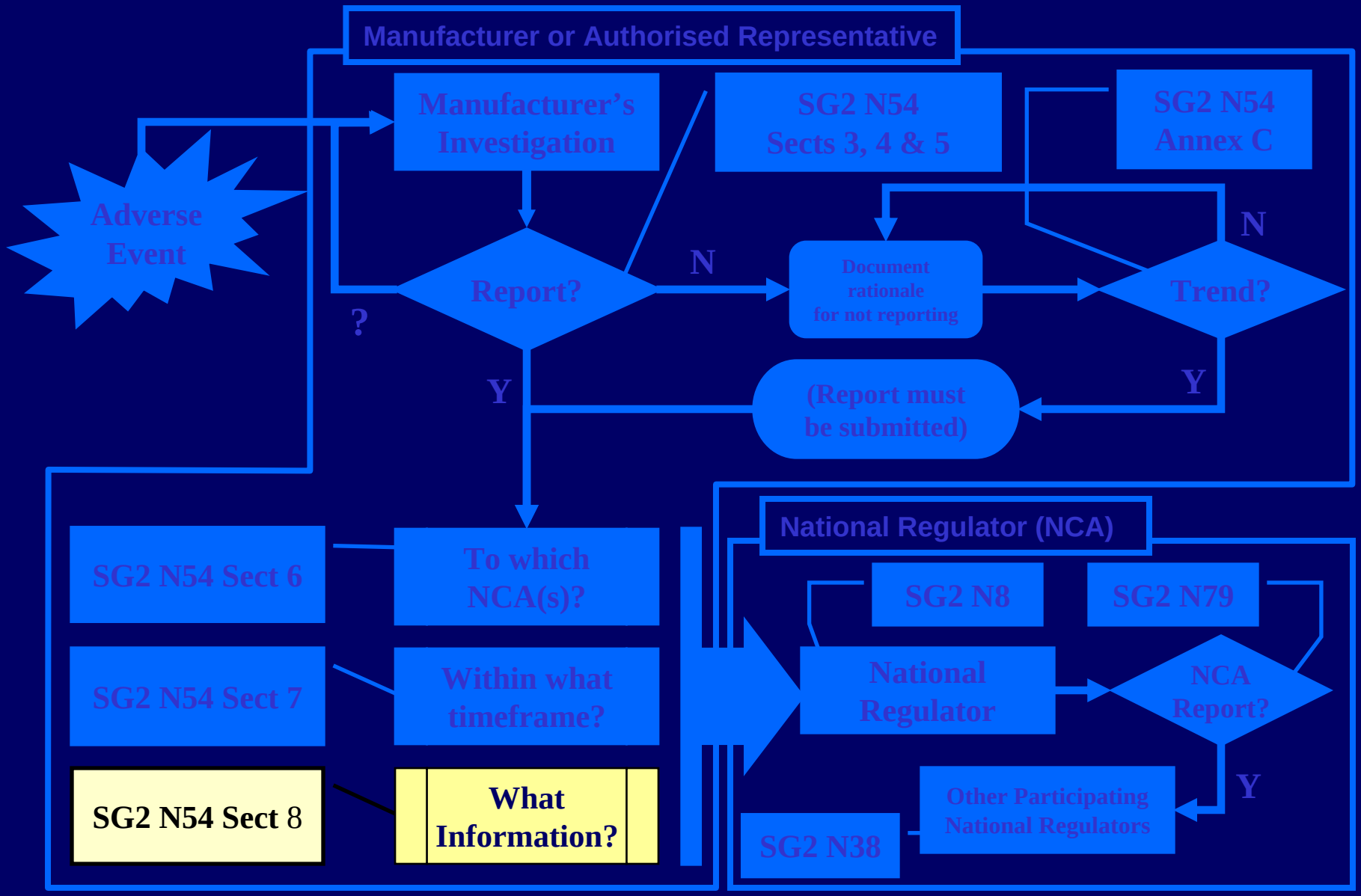
Reporting Timeframes

- **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

- **<u>Unanticipated:</u>** 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

Case study:

Implementation of SG2 Adverse Event Reporting Guidance in Europe

Changes Required

- The way that **YOU** and your agency thinks about regulation.
- Then change:
  - The Law
  - The Regulations (legal instruments)
  - National guidelines
  - Administrative practice

Situation in Europe

- Directives are addressed to the Member States (MS)
- Changes are lengthy and difficult as 27 MS plus the European Commission (EC) are around the table
- Guidance document has been created with participation of industry, MS and the European Commission

Basic Reporting Criteria, Exemptions 1-3

N54 Part	Description	Status in Europe
Sections 3.1-3.3	Definition of reportable event, basic reporting criteria	Implemented in the MEDDEV
Exemptions *		
Section 4.1	Deficiency of a New Device Found by the User Prior to its Use	Implemented, but MEDDEV says "always instead of "normally".
Section 4.2	Adverse Event Caused by Patient Conditions	Implemented in the MEDDEV
Section 4.3	Service Life of the Medical Device	Implemented in the MEDDEV; shelf life to be specified in the technical file

* The MEDDEV talks about conditions where reporting under the medical devices vigilance system is not ususally required

Exemptions 4-8

N54 Part	Description	Status in AU
Section 4.4	Protection Against a Fault Functioned Correctly	Implemented in the MEDDEV
Section 4.5	Remote Likelihood of Occurrence of Death or Serious Injury	Implemented in the MEDDEV
Section 4.6	Expected and Foreseeable Side Effects	Implemented in the MEDDEV, minor wording changes
Section 4.7	Adverse Events Described in an Advisory Notice	Implemented in the MEDDEV
Section 4.8	Reporting Exemptions Granted by NCA	Implemented in the MEDDEV

Other Sections

SG2 Doc	Description	Status
Section 5	Use Error Exemptions	implemented in the MEDDEV
Section 8	Universal Dataset	Implemented in the MEDDEV
Section 7	Timing for Adverse Event Reports	"Serious public health threats" immediately but not later that 2 days after recognition; Death or unanticipated serious injury" immediately but not later than 10 days after mfr's awareness All other reports immediately but not later than 30 days after mfr's awareness
Annex C	Trending of Adverse Event Reports	Implemented, in the MEDDEV

Conclusions:

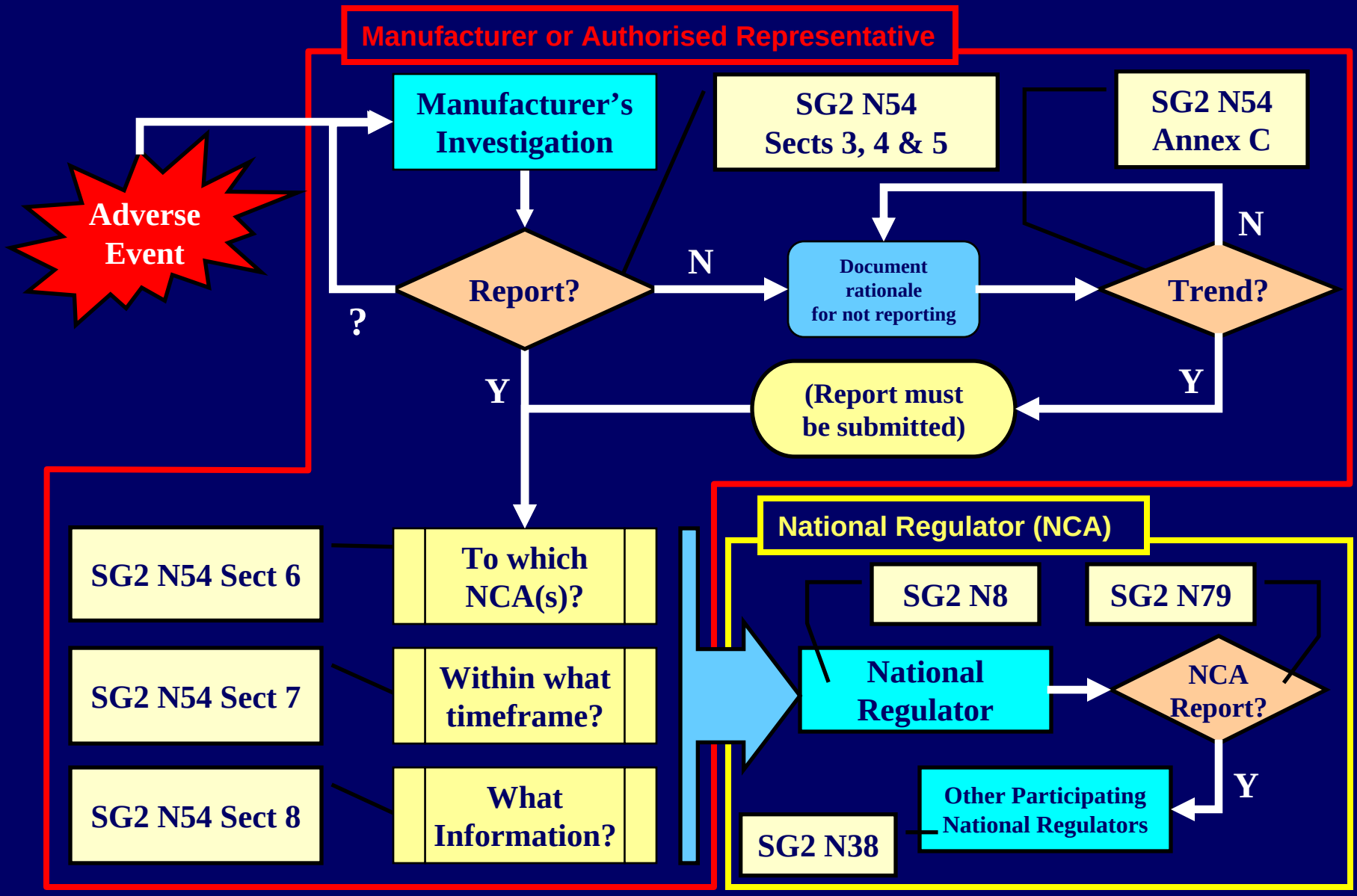
- Was it easy?.....NO
- Was it hard work?.....YES

- Was it worth the trouble?.....YES!

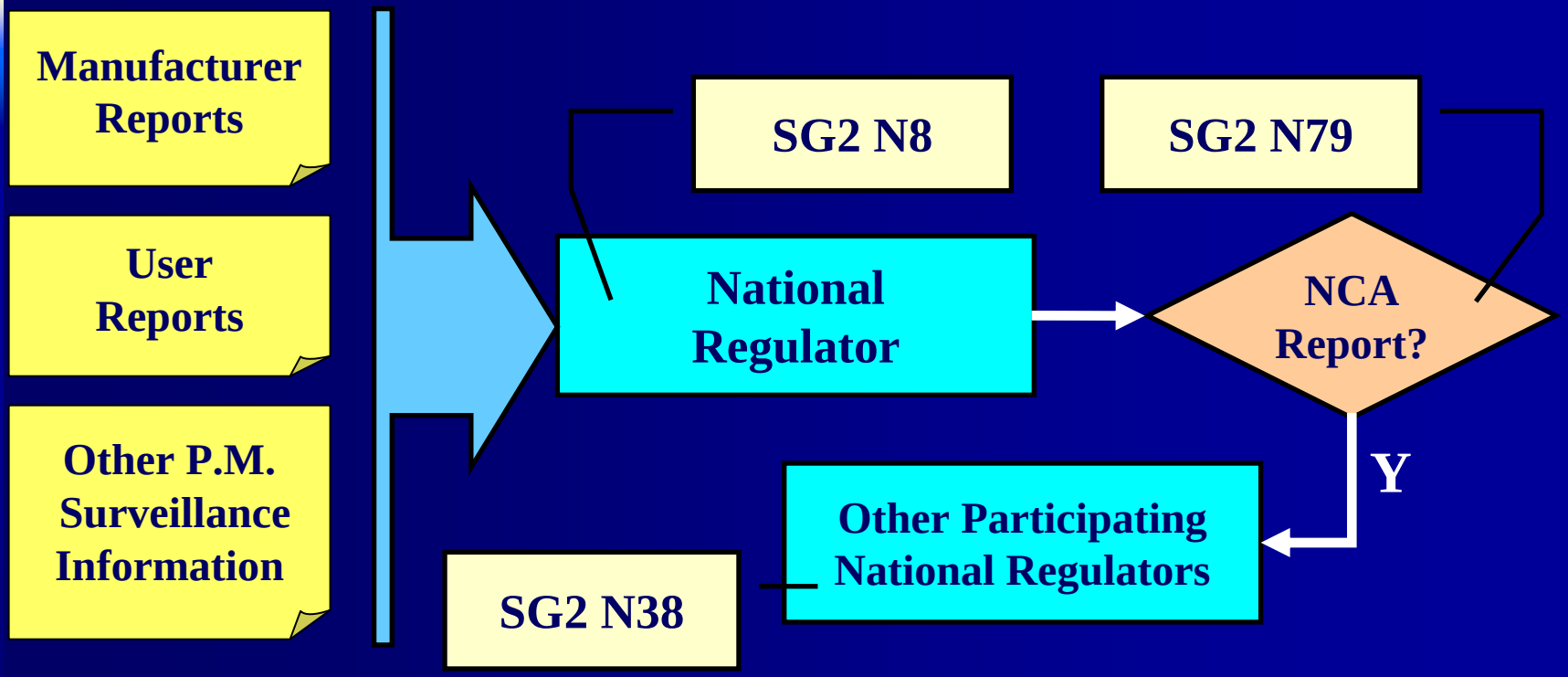
GHTF SG2:
National Competent Authority Report Program

Ekkehard Stösslein – BfArM Germany
Jorge Garcia – TGA
Mark Segstro – Health Canada
Deborah Yoder – FDA

Map of SG2 Guidance on AE Reporting



Handling Adverse Event Reports:
NCA Systems



Handling Adverse Event Reports:
Risk Assessment

RISK = Incidence x Hazard

- A hazardous event that occurs infrequently constitutes a LOW RISK
- An event that occurs often but has few or no safety implications constitutes a LOW RISK

Handling Adverse Event Reports:
Risk Assessment for public servants

- There may be other factors that affect the outcome of risk assessment.
- These may be local or global considerations.

RISK = Incidence x Hazard x Public Concern

Handling Adverse Event Reports:
Risk versus Benefit

- What “toll” is the public willing to pay for the benefit of using:
  - Pacemakers? - Heart valves?
  - Hip implants? - Catheters?
- Does the “risk taker” benefit from taking the risk?

Handling Adverse Event Reports:
Risk Assessment

- There is no “silver bullet”
- Every ISSUE should receive individual risk assessment
- When difficult, seek help:
  - Medical experts
  - Other regulators
  - Manufacturer

Handling Adverse Event 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

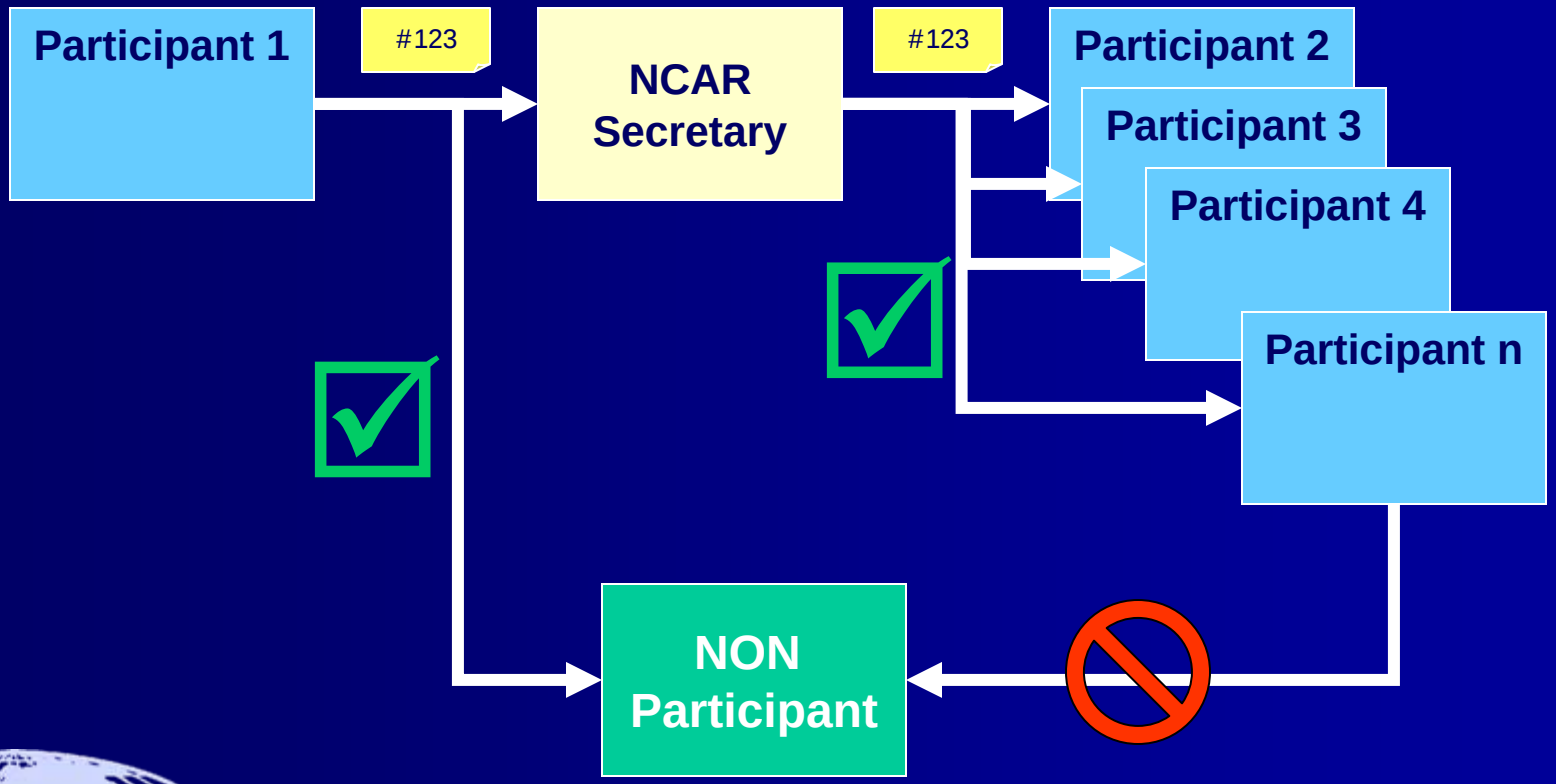
Participation:
Commitments

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



Submitting a Report:
Criteria for Reporting & Form

NCAR Criteria & Reporting Form

- Most of the information provided during this session is available in document N79R8:2006 at www.ghtf.org/sg2/final

Getting started

An NCAR tells other regulators about device issues that they do not already know about

There are 10 criteria *to consider* before generating an NCAR

NOTE: Criteria considerations can clarify that no NCAR is needed

1. Consider : Seriousness not serious = no NCAR

Seriousness is determined by:

- A technical or clinical assessment
- The actual or potential impact to patients and users
- The difficulty in recognizing the issues and how to prevent or mitigate them

2. Consider : Unexpectedness by itself = no NCAR

Unexpected because of:

- a lack of historical information; rare
- an increase in frequency of occurrence
- a change in the situation in which it's occurring
- a change in the outcome

3. Consider: Vulnerable Pop.

Is any special population at increased risk for adverse events?

If yes, can you define it? Such as:

- Age related – pediatric, geriatric
- Immune status – pregnancy, illness

4. Consider: Preventability

Can the issue be prevented or minimized?

Do you have recommendations for preventing or minimizing the issue?

5. Consider: Public Percept.

Sometimes the public perception* of an issue makes it appear “serious”

*All NCARs should be perceived as or considered “serious”

6. Consider: Risks & Benefits

Do established risks and benefits related to the device address the issue?

Are there well recognized and established standards of practice related to the use of the device?

Are there alternative devices available for use?

7. Consider: Lack of Data

Do you have scientific data on long term effects?

Do you have baseline data for comparison?

Is there national or international consensus on the issues and their resolution?

8. Consider: Repeated issues

- Has this issue been identified before?
- What new information do you have to share?
- How will a new NCAR change what is already being done?

9. Consider: Written notifications already exist

No NCAR is needed when the issue is already well published and publicly available.

An NCAR might be appropriate when you get new information that is not otherwise publicly available.

The new information should be clearly described and easily found.

10. Consider: How will the NCAR help?

When the manufacturer's efforts are sufficient = no NCAR

When you have no new information about the issue = no NCAR

When you have identified a new serious device issue, or have additional information of regulatory significance = send NCAR

The final decision is yours

Ultimately each regulator decides if and when to send an NCAR.

Too many NCARs = loss of attention

Too few NCARs = loss of information

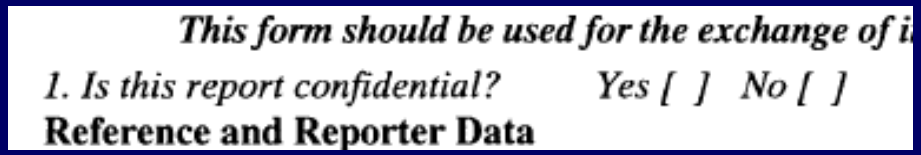
About the NCAR document

An NCAR is for exchange of information between NCAR participants only, and should not be made public.

The NCAR format provides for consistency and familiarity with reported information.

Use “NA” in boxes where data is not applicable

1. Is this report confidential?


This form should be used for the exchange of i

1. Is this report confidential? *Yes [ ] No [ ]*

Reference and Reporter Data

Check Yes [x] only when the NCAR has information that is not already public.

If the NCAR includes both public and confidential information, clearly identify what information is considered confidential.

2. The permanent NCAR Reference

2. NCA report ref. no.:

Assigned by the originating regulator:

- Always begin with your 2 letter ISO* Country code (*see ISO 3166)
- Add –YYYY-MM-DD- for the year, month and day
- Last is the 3 digit sequence number; start each new year with 001

E.g., DE-BfArM-2008-10-08-030

Additional Ref #s

3. Local NCA reference no.:	4. Related NCA report nos.: (if any)	5. Manufacturer Ref/Recall no.:

3. Local NCA # = national tracking #
4. Related NCAR # = list of any NCARs sent on the same issue
5. Mfr Ref/Recall No = internal tracking # relating to corrective action or recall

Reporter Data

6. Sent by: (Name and Organization)	7. Contact person: (if different fr

8. Tel:	9. Fax:	10. E-mail:

6. Sent by = who sent the NCAR
7. Contact person = who will answer any questions, if not #6.
8 – 10. Telephone, Fax, and E-mail information = how to reach the person who can answer any questions about the NCAR

Device Data

11. Generic name/ kind of device:	12. Nomenclature id:	13. No.:

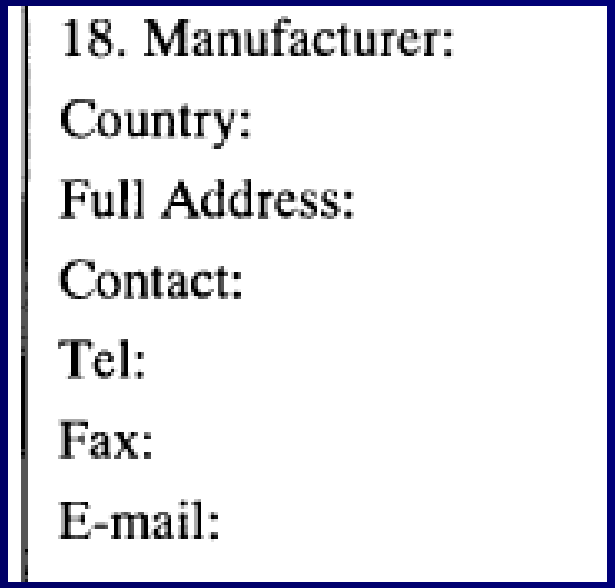
11. Generic name/ kind of device = a general & short device descriptor ; e.g., defibrillator; wheelchair; suture
12. Nomenclature id = the name of the coding system you use, if any
13. No. - the specific code number for the subject device, if any

More Device Data

14. Trade Name and Model:	15. Software version:	16. Serial no.:	17. Lot/batch no.:

14. Trade Name & Model* = common product identifiers. **Note: 25c. also asks for other trade names used*
15. Software version – e.g., FreeWare V2.1
16. Serial No.: & 17. Lot/batch No.: = unique product identifiers

18. Manufacturer Info.

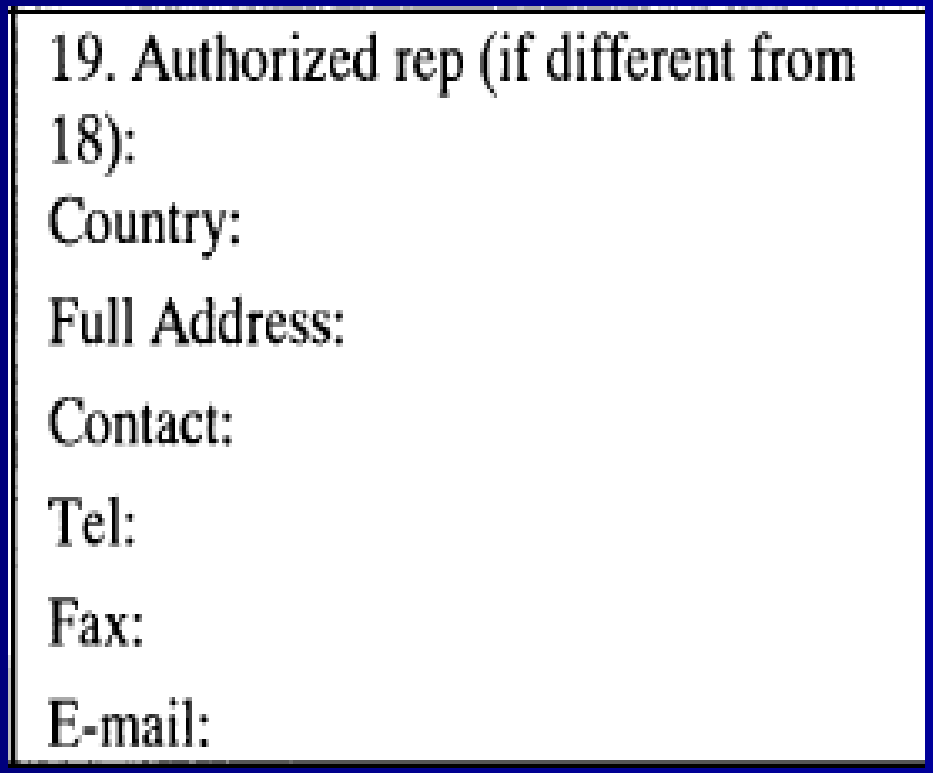

18. Manufacturer:
Country:
Full Address:
Contact:
Tel:
Fax:
E-mail:

Informs:

- who made the device,
- where the device was made, and
- a contact at the manufacturer

19. Authorized Rep. Info.

Optional: Use only when contact information is different from 18.


19. Authorized rep (if different from 18):

Country:

Full Address:

Contact:

Tel:

Fax:

E-mail:

20. CAB/Notified Body no.

CAB = conformity assessment body

Conformity assessment includes testing, inspection and certification of products, processes and persons.

Notified bodies carry out the tasks pertaining to the conformity assessment procedures

21. Device approval status & Risk Class

21a. Device approval status = the device was or was not approved for marketing

21b. Risk Class* = the device is classified as a low, medium or high risk.

**Risk Class is not globally harmonized at this time. Generally, the higher the risk- the higher the risk class #.*

22. Action Taken

Action taken identifies what the NCA or the MFR has done.

- Check all boxes that apply.
- Use the “other” option as needed, and include a brief description

7. Action taken:
[ ] None
[ ] Safeguard Action
[ ] Field Safety Corrective Action
[ ] Other (specify)

Event Data

23a. Background and reason for this report = Description of what the device issues are and what impact they have on patients or users

23b. Investigation complete? Y or N -

Confirms if the investigation about the reported issue is complete or not

More Event Data

24a. Conclusions = the findings of the device investigation. Attach any documents and include web addresses when possible

24b. Have the manufacturer's actions been made public? Y or N

24c. Tells if you will coordinate the investigation - Y or N

Recommendations & global information

25a. Recommendations = what you want recipients to do with the information

25b. Known to be in the Market… = a list of countries where device is known to be marketed

25c. Also marketed as = list names different from #14.

Report distribution

NCAR Secretariat: MDV@hc-sc.gc.ca

26a. Mark all that apply.

This report is being distributed to:

[ ] The NCAR Secretariat for further distribution to FULL NCAR PARTICIPANTS.
[ ] The NCAR Secretariat for further distribution to ALL NCAR PARTICIPANTS.
[ ] EEA states, EC, and EFTA
[ ] The following targeted NCAs:
[ ] The manufacturer / authorized rep.:

26b. Complete only when your NCAR #s are not sequential

26b. The last GHTF-NCAR distributed by this NCA was (>>>>

NCAR Program:
Procedures and Statistics

NCAR Exchange Program - Procedures

- NCA Report number format: CC-YYYY-MM-DD-###, where:
  - CC is the 2-letter ISO code for the NCA
  - YYYY-MM-DD is the year-month-day
  - ### is the sequential numeric identifier for the report

NCAR Exchange Program - Procedures

- Submit to NCAR Secretariat (NCAR-Sec) at GHTF.NCAR@tga.gov.au
- Prefer N79 form, MS-Word (.doc) format
- NCAR-Sec reviews report:
  - NCA Report Number correct?
  - Previously submitted? Other errors?

NCAR Exchange Program - Procedures

- 2 mailing lists:
  - NCARs originating in Europe
  - NCARs originating in AU, CA, HK, JP, US
- Forwarded with filename:
  CC-YYYY-MM-DD-###_Company-Name_Device-Name.doc

NCAR Exchange Program - Procedures

- NCARs may be:
  - For your information
  - For your action
    - Recalls, Corrective Actions
    - Safety Alerts
    - Confidential requests from an NCA for information concerning an investigation

NCAR Exchange Program - Procedures

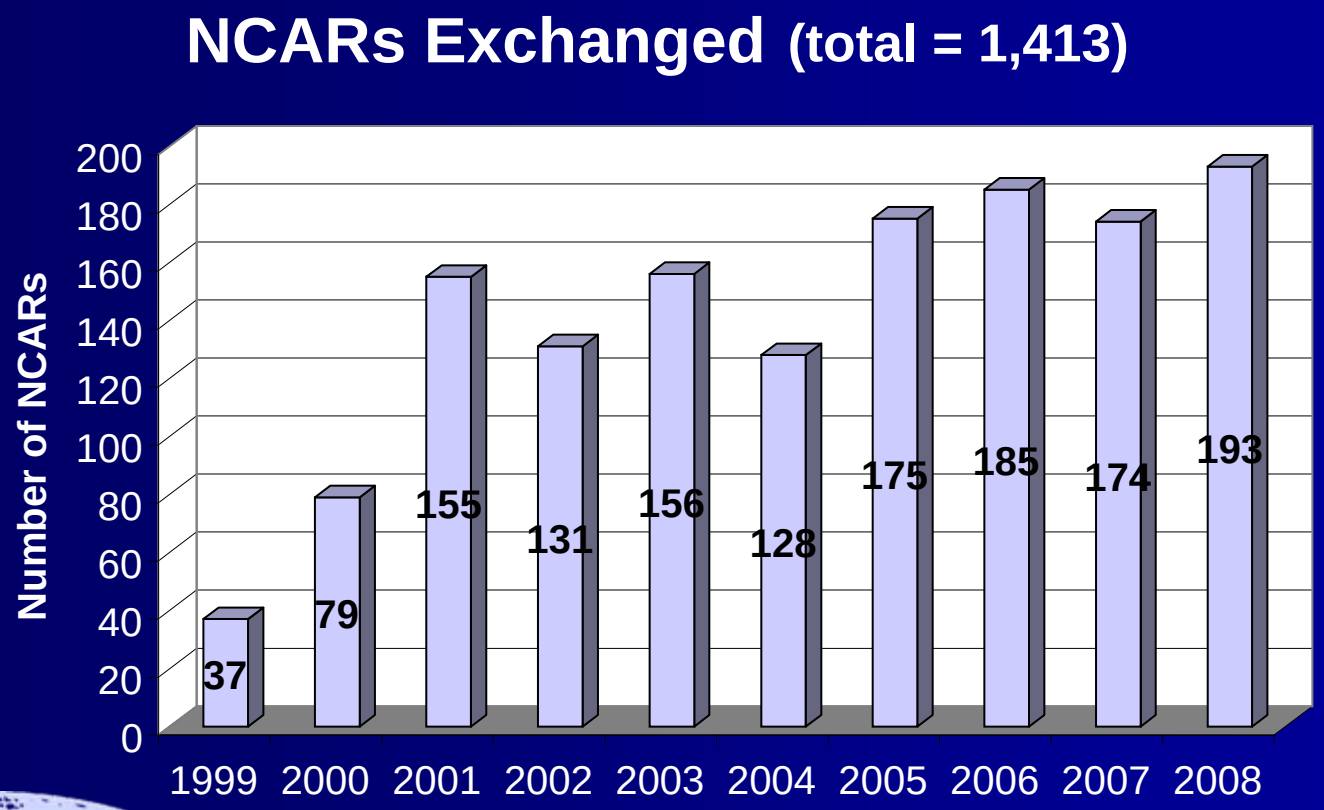
- You must not:
  - Release the information outside your NCA
  - Publish the information on the internet
  - Contact the company for info, if NCAR confidential

NCAR Exchange Program - Procedures

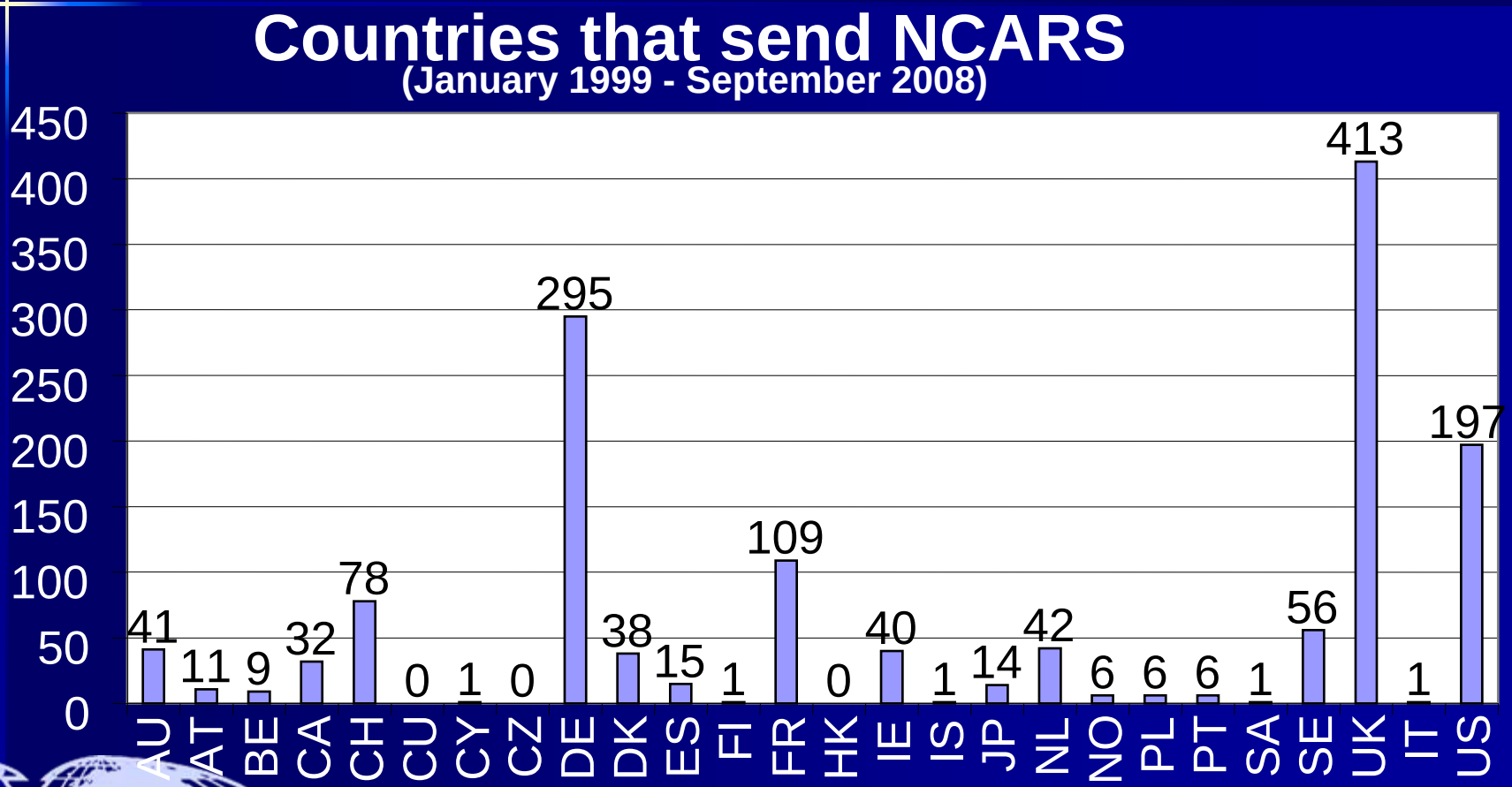
- Important notes:
  - Single point of contact for NCA
  - Responsibilities
  - Field 1, Confidentiality
  - Extent of device distribution

NCAR Exchange Program - Statistics

NCAR Exchange Program - Statistics



NCAR Exchange Program - Statistics



NCAR Exchange Program - Statistics

- Cardiovascular – 290 NCARs (20.5 %)
- General Hospital – 213 NCARs (15.1%)
- Orthopaedics – 120 NCARs (8.3 %)
- General/Plastic Surgery – 110 NCARs (8.0 %)
- Radiology – 97 NCARs (7 %)
- Anaesthesia – 92 NCARs (6.5 %)

Thanks for Your Attention!

Questions??

GHTF SG3 Training (Quality Systems)
APEC Funded Seminar
on
Harmonization of Medical Device Regulations

Toronto, Canada, May 14 - 16, 2009

Egan Cobbold, Chair SG3
Gunter Frey, Vice-Chair SG3

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
6. Supplier Control

GHTF SG3 – Role, Members, Documents

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 (2009)

Australia

Mr Ken Nicol	MIAA/St. Jude
Mr Keith Smith	TGA/OMQ

Canada

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

European Union

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

Japan

Mr Hideki Asai	JFMDA/Hitachi
Mr Munehiro Nakamura	JFMDA/Kaneka
Mr Nagai Hirotada	MHLW
Ms Noriko Okuyama	MHLW
Mr Tsutomu Makino,	PMDA

United States of America

Ms Kimberly Trautman	FDA
Mr Gunter Frey	NEMA/GE (Vice-Chair)
Mr Ken Kopesky	AdvaMed/Medtronic

AHWP

Mr Ali Al Dalaan	Saudi FDA
Mr Ronald Goon	Singapore (J&J)

SG3 Documents – the present

Since 1992, the study group has prepared and published five guidance documents. Three 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 System - Process Validation Guidance.

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

SG3/N17/2008 Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers

SG3 Documents – the present

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

When required, the study group will work collaboratively with other study groups or *ad hoc* groups on projects like combination products, regulatory auditing, changes etc.

SG3 Documents – the future

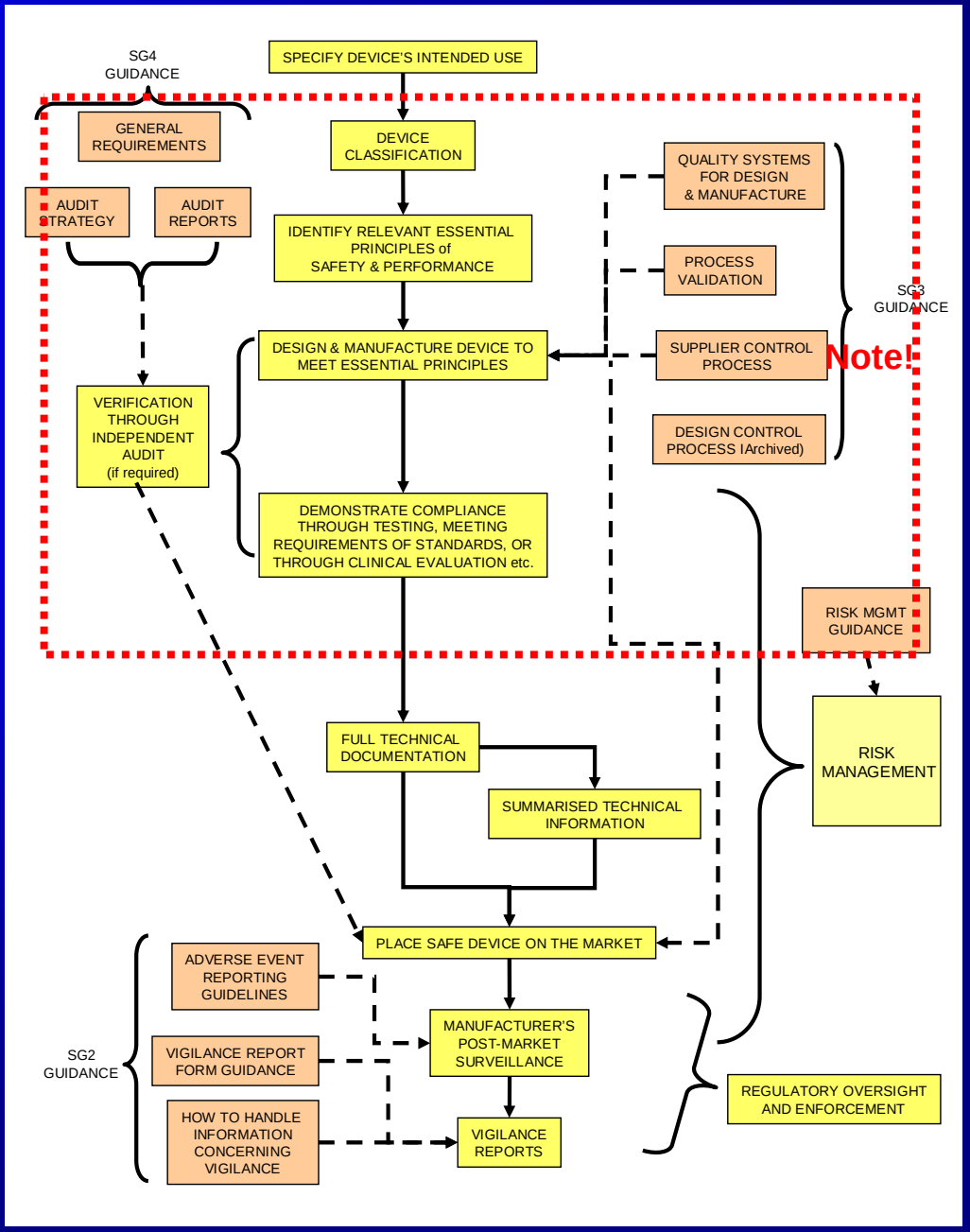
Study Group 3 is currently working on two new guidance documents :

- Document N18 - corrective and preventive action (CAPA) principles and activities" (and
- Document N19 - characterizing the significance of quality management system deficiencies

In the next couple of years the study group will do more work with ISO Technical Committee 210 / Working Group 1 on the expected revisions to ISO 9001:2008, ISO 13485:2003 and ISO/TR 14969:2004

SG3 Documents – the future

All future work of SG3 will be strongly influenced by the work the Steering Committee is presently doing on topics like the "Global Harmonization Task Force Medical Device Regulation Model"



Quality Management Systems: History and Evolution

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?

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

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

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 products 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 -

Key sections of ISO13485:2003

Section 1.0 - Scope

Section 2.0 - References

Section 3.0 - Definitions

Section 4.0 - Quality Management System Requirements

Section 5.0 - Management Responsibility

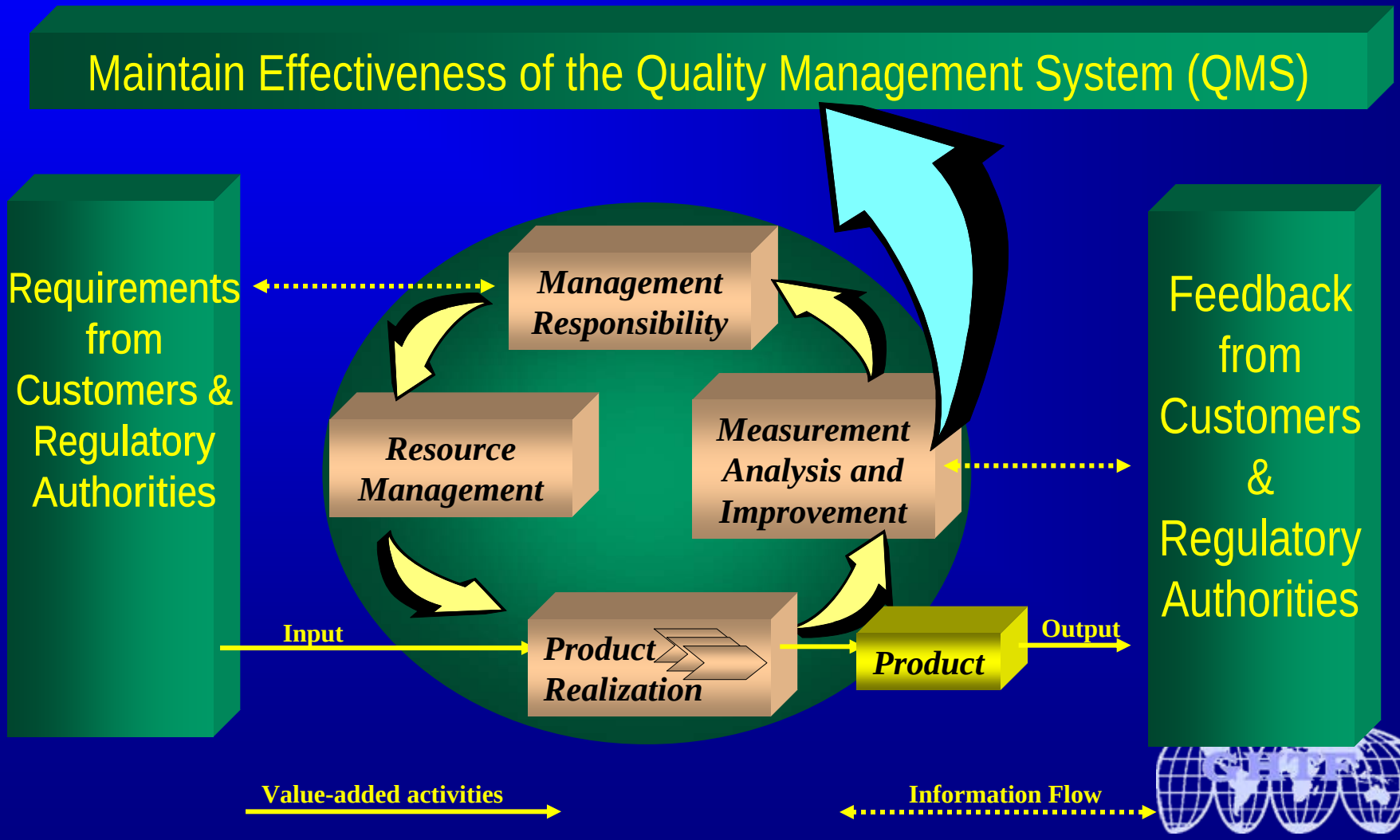
Section 6.0 - Resource Management

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 "type and extent of 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.)

GHTF SG3 N17 Guidance on the Control of Products and Services Obtained from Suppliers

- ISO 13485 requires the organization to control products and services obtained from suppliers.
- The type and extent of controls are to be established and documented within the organization's quality management system.
- Control could be defined and documented in the form of contractual arrangements, quality plans or other types of documents.

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

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)

5.5 Responsibility, authority and communication

- Documented position descriptions, including responsibilities and authorities, organization charts
- One management representative - designated by top management! Ensures promotion and awareness of regulatory and customer requirements throughout organization

5. Management Responsibility

5.6 Management Review

- Periodic assessment of the QMS for continued suitability, adequacy and effectiveness.
- **Inputs include:**
  - results of audits; changes that could affect the quality management system; recommendations for improvement; and, new or revised regulatory requirements.
- **Outputs include:**
  - improvements needed to maintain the effectiveness of the quality management system and its processes; improvement of product related to customer requirements; resource needs

6. Resource Management

6.1 Provision of resources

- People; infrastructure; work environment; information; suppliers and partners; natural resources; financial resources

6.2 Human Resources

- Personnel performing work affecting product quality and device safety and effectiveness must be competent. Organization must be able to demonstrate this!

6. Resource Management

6.3 Infrastructure

- Buildings; work space; utilities (water, electricity, waste management, etc.); process equipment (software and hardware); Equipment maintenance activities & frequency; Supporting services (cleaning, etc.)

6.4 Work Environment

- Significant factors within the work environment that can affect product quality are process equipment, established work environment (controlled environments, clean rooms, etc.), personnel.

7. Product Realization

7.1 Planning of product realization

"Product realization" describes the processes starting with

- Planning (7.1)
- determination of customer requirements (7.2)
- 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 inform device manufacturers on how best to integrate ISO 14971 into a QMS like ISO 13485:2003.

7. Product Realization

7.2 Customer-related processes

Focus is on product and services to be supplied.

- Requirements related to the product like regulatory or legal requirement, design related factors included in customer orders, unspecified customer expectations.

- Review of post-marketing product performance like customer complaints and advisory notices

7. Product Realization

7.3 Design and development

Design and development planning (7.3.1)

- Established procedures describing design processes and ALL design activities

Design and development inputs (7.3.2)

- Intended use, physical characteristics, regulatory requirements, customer training, manufacturing processes, lifetime, etc.

Design and development outputs (7.3.3)

- Drawings and parts list, finished device, manufacturing and inspection procedures etc.

Design and development review (7.3.4)

- Does design satisfy specified requirements, functional requirements, environmental conditions?

7. Product Realization

7.3 Design and development

Design and development verification (7.3.5)

- Ensure that design outputs conform to specified requirements (i.e. design inputs)

Design and development validation (7.3.6)

- Ensure that the medical device meets user requirements and intended use (validation performed on production or production equivalent units)

Control of design and development changes (7.3.7)

- Evaluate effect of change on parts and product already delivered. Ensure changes are approved before implementation (regulatory, manufacture etc.)

Guidance Document SG3N17
"type and extent of control".

7. Product Realization

7.4 Purchasing

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!

7. Product Realization

7.4 Purchasing

Purchasing information describes the product to be purchased in sufficient detail.

- technical information and specifications, test and acceptance requirements, quality requirements for products, services, and outsourced processes, regulatory requirements, etc.

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 provision (7.5.1)

- Ensure cleanliness of product and contamination control, control installation, documented procedures for servicing, maintain records and process parameters for sterilization processes, etc.

Validation of processes for production & service is required where the resulting output cannot be verified. (7.5.2)

- Validate software used in production and service delivery and maintain records.
- Validate device sterilization processes prior to initial use.

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

7. Product Realization

7.5 Production and service provision

Identification is required throughout the product realization process (7.5.3).

- Raw materials; components; finished medical devices, etc.

Traceability (when required) allows for identification of the history or location of a product or activity by recorded identification (7.5.3):

- Forward to customers (a.k.a “device tracking”) ; backward to raw materials, components,, etc.

Customer property is defined as property or assets owned by the customer and under control of the organization. (7.5.4)

Preservation of product applies throughout product realization. (7.5.5)

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, internal & external audits etc.

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

- document the existence and root cause of the nonconformity
- define and implement 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, supplier performance, product conformance, trends of processes & products, feedback, etc.

8. Measurement, analysis and improvement

8.5 Improvement

Establish procedures to issue and implement advisory notices at any time and to notify regulatory authorities of adverse events.

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,
- Immediate correction of problem (if appropriate)
- 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 "eliminate causes of ***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.

Summary

- History of quality management system
- Key Sections of ISO 13485:2003
- Links between SG3 guidance documents and ISO 13485
- Output of an effective QMS

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

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

- 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.

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

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

- 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.

SG3/N15R8/2005 "Implementation of Risk Management Principles and Activities Within a 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.

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

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

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

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.

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

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.

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

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.

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

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.

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

Risk control and monitoring activities:

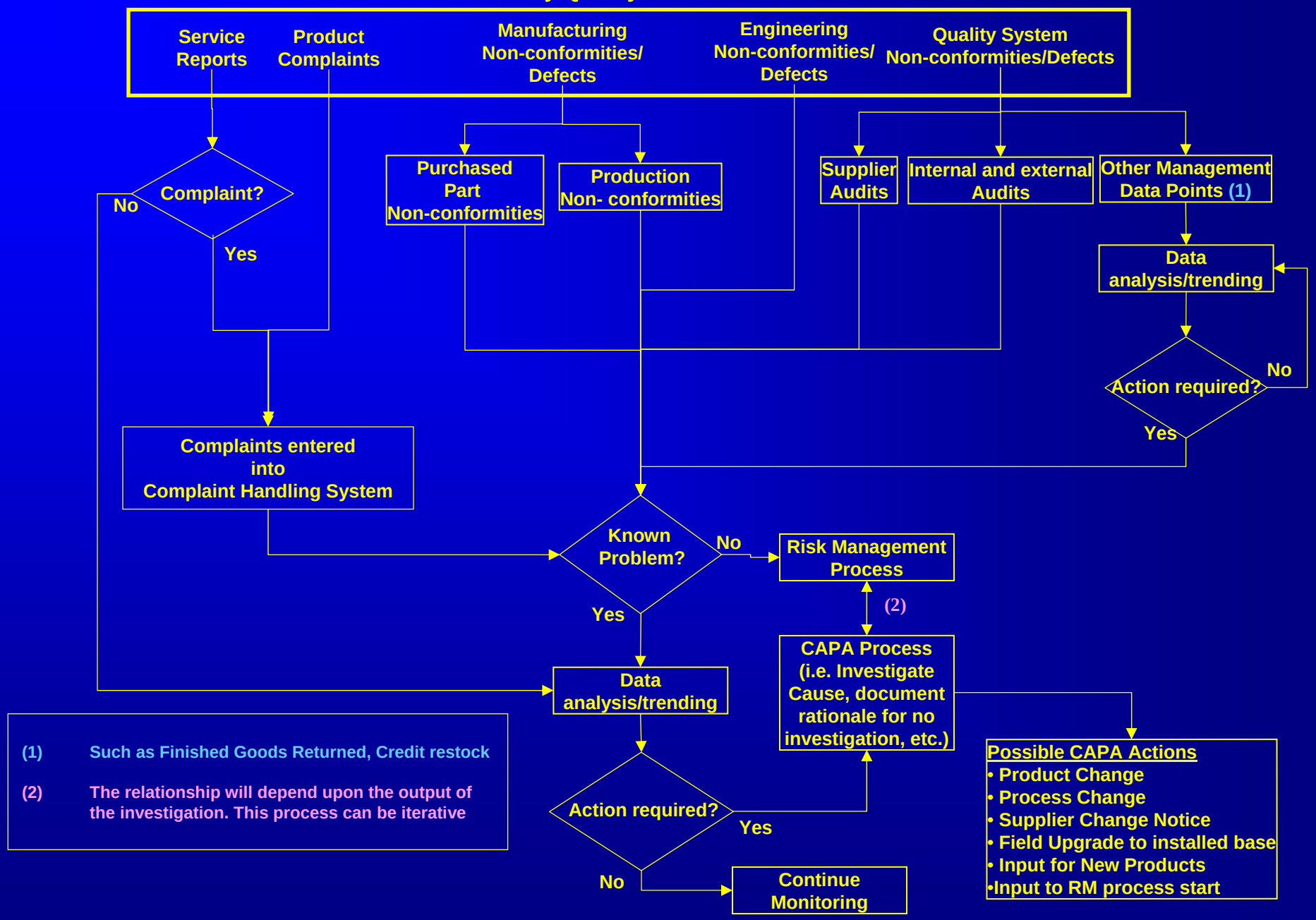
- Throughout the life-cycle of the device the manufacturer monitors whether the risks continue to remain acceptable and whether any new hazards or risks are discovered.
- An effective and well defined Quality Management System is key!

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

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.

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

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!

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

Risk Management needs to be procedurally tied into processes of QMS:

- Design Controls
- Purchasing procedures and criteria
- Acceptance Activity procedures and criteria
- Manufacturing activities
- Process validations
- Rework procedures and decisions
- Corrective and preventive actions

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]

- **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]

- **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]

Summary

- Key features of SG3/N15R8/2005 “Implementation of Risk Management Principles and Activities Within a Quality Management System

- How to implement RM principles into a QMS

Process Validation Guidance
GHTF/SG3/N99-10:2004
Study Group 3

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

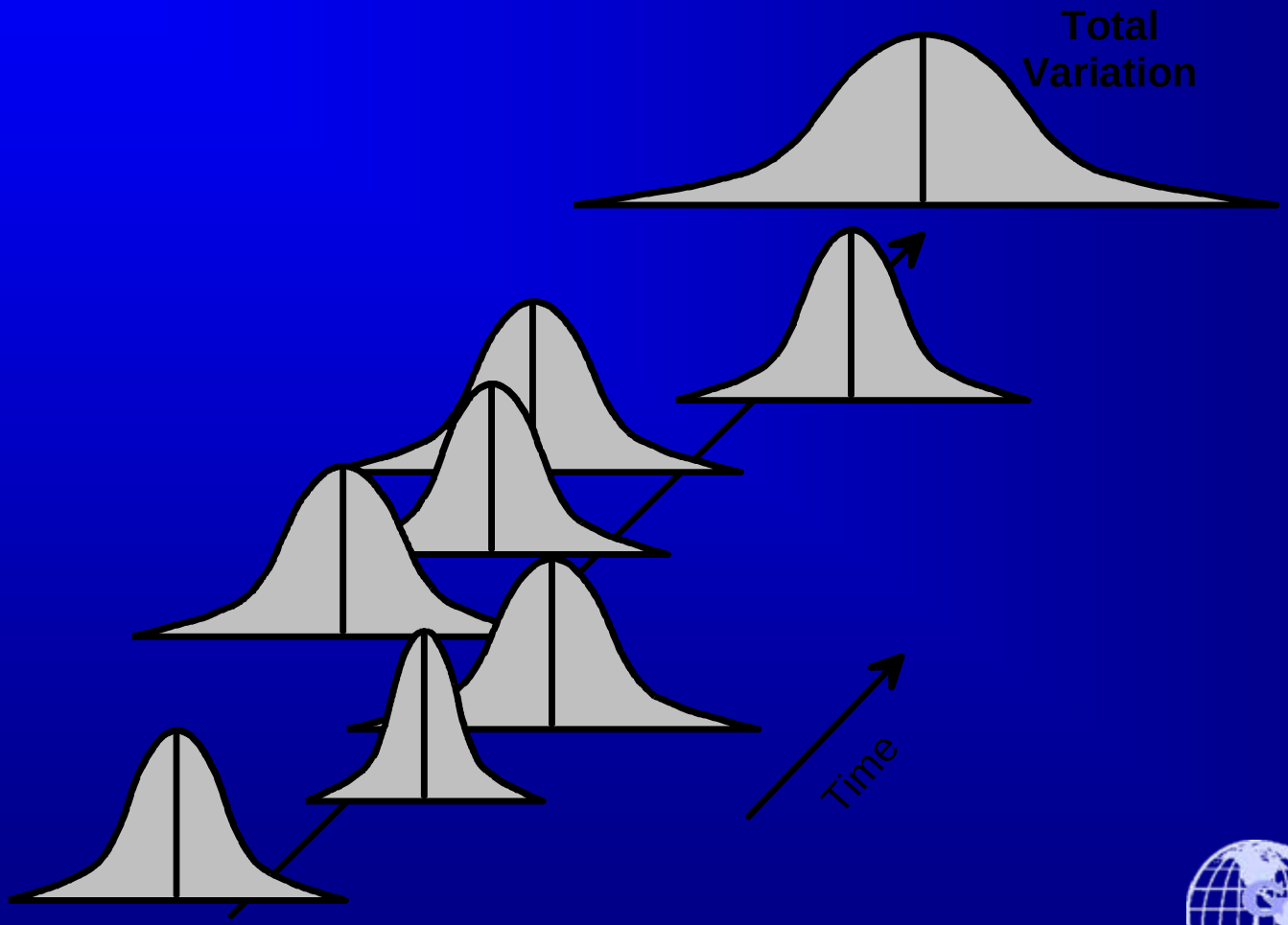
- Things that should be Established:
  - Procedure
  - Process control limits
  - Output specifications
  - Alert levels and action levels
  - Specifications for components, manufacturing materials
- Environmental conditions that may affect process stability
  - Temperature
  - Humidity
  - Light
  -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

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

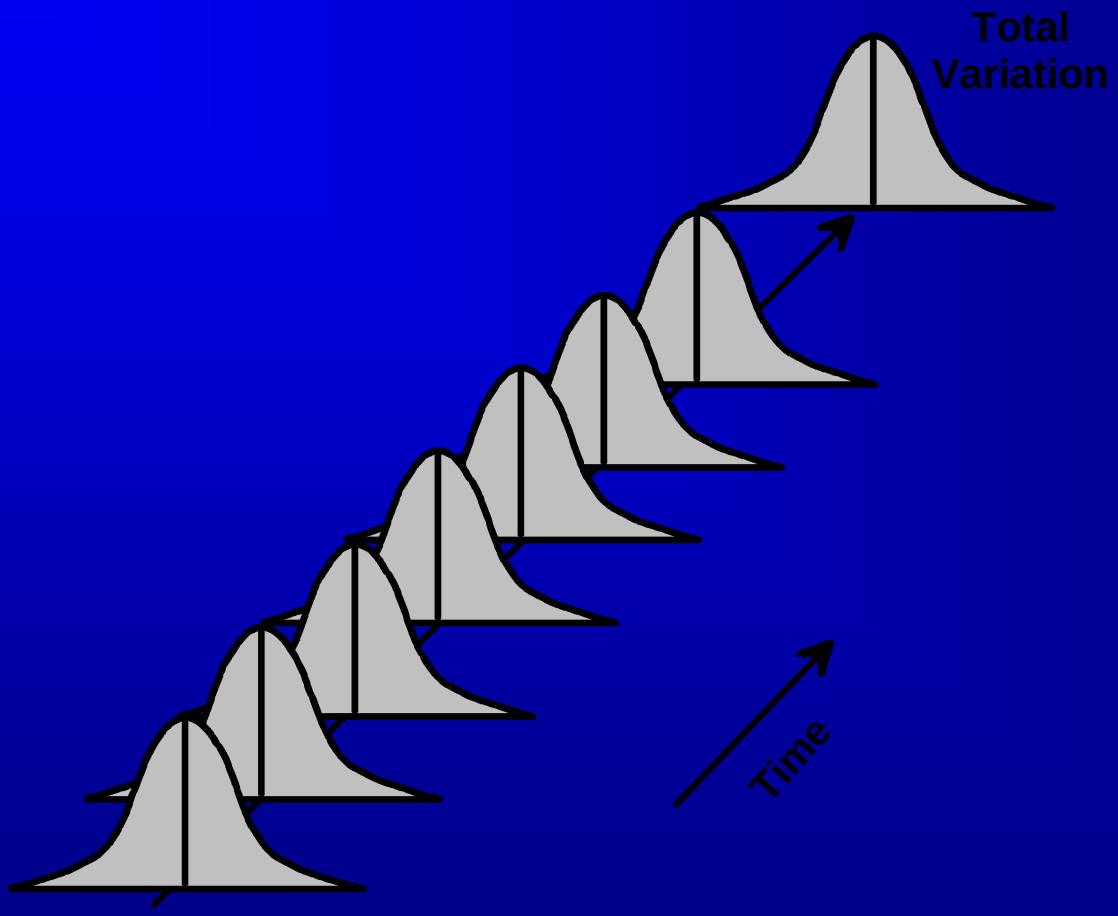
Performance Qualification (PQ)

- 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) 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://www.newapproach.org/Directives/DirectiveList.asp

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

GEHC Internal sites:

Americas: http://supportcentral.ge.com/products/sup_products.asp?prod_id=23217
Europe: http://gein.euro.med.ge.com/engineering/qualsys/
Asia: http://3.28.123.6/free/qmc/qasr/newQASRasia/

Additional information (cont.)

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices Official Journal L169, 12/07/1993 P. 0001 - 0043 can be found at:
http://3.70.4.1/~qualsys/regulatory/MDD/1993L0042_consolid.pdf

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:	not available at time of this writing
Fax:	not available at time of this writing
E-Mail:	jisc@meti.go.jp
Web Site:	http://www.jisc.go.jp/eng/

GHTF SG3 Training (Quality Systems)
APEC Funded Seminar
on
Harmonization of Medical Device Regulations

Toronto, Canada, May 14 - 16, 2009

Egan Cobbold, Chair SG3
Gunter Frey, Vice-Chair SG3

SG3/N17R9/2009 "Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers "

- A Status Update and Introduction -

Study Group 3

- GHTF Final Guidance
- **Title:** Quality management system – Medical devices - Guidance on the control of products and services obtained from suppliers.
- Document available at:

  http://www.ghtf.org/documents/sg3/sg3final-N17.pdf

Control of Suppliers

- When a medical device manufacturer chooses to utilize suppliers, the manufacturer should ***ensure control over any product or service obtained*** from such suppliers as defined within the quality management system (QMS).
- This ***extends further if the supplier sub-contracts work***.

Scope

- A product or service is one which is purchased **or otherwise received** by the manufacturer.

- A supplier is anyone that is independent from the manufacturer's quality management system.

Scope of Quality Audit/Internal Audit

- This includes a supplier that may be part of the manufacturer's organization but operates under a separate quality management system.

- In other words, if the supplier is not a part of the manufacturer's internal audit (quality audit) scope, then the supplier is under a separate quality management system and is considered an internal supplier. *(Note: These quality management systems may be identical!)*

Scope of Quality Audit/Internal Audit

- Corporations or companies that have corporate quality policies and procedures do not necessarily place all divisions or groups under the same quality management system.
- One division or group can be an internal supplier to another division or group within the same corporation/company.

Internal suppliers are to be controlled in a similar way as external suppliers are controlled.

Internal Suppliers

- The controls for internal suppliers are not necessarily handled through Purchase Orders, Contracts, or the like, but instead other types of control mechanisms such as
    - internal agreements
    - procedures or
    - quality plans.

Manufacturer's Responsibility

- The "manufacturer" or entity, that has the ultimate responsibility for its quality management system, cannot relinquish (contractually or otherwise) its obligation and responsibility over any or all functions within the quality management system. This means **the <u>responsibility</u> for complying with the quality management system requirements cannot be delegated to any supplier** (internal or external) of products and services.

Regulatory Audits

- Regulatory authorities and third parties will inspect/audit a manufacturer to confirm that **objective evidence of control over products and services** from suppliers is **present, or readily available, at the manufacturer's site**.
- **Failure to have any evidence** on-site, or provide access to any objective evidence **of the controls** associated with products and services from suppliers **could result in the manufacturer's quality management system being non-compliant.**

Six Phases of Supplier Controls

- The process of establishing controls for products and services obtained from suppliers typically comprises six phases, which include:
  - Planning
  - Selection of potential supplier(s)
  - Supplier evaluation and acceptance
  - Finalization of controls and responsibilities
  - Delivery, measurement and monitoring
  - Feedback and communication, including Corrective Action and Preventive Action processes

Planning

In establishing the controls for product and services obtained from suppliers, it is expected that planning initiates the process.

The output of this activity may be in the form of design and development plans, quality plans, purchasing plans, etc., as defined in the manufacturer's QMS.

Planning

Objective evidence may include:

- Identification of the product and services to be obtained. This can be a general description or a specification, if already available.
- Product and service requirements/specifications for parts, materials, process, software, environment, testing, etc.
- QMS process requirements, such as procedures/work instructions for adverse event reporting, QMS auditing, clinical monitoring, design, manufacturing, calibration, maintenance, verification activities, record keeping, etc.

Planning

Objective Evidence may include (continued):

- Name(s) and contact information of potential supplier(s).
- Documented list of the risks identified.
- Although not a regulatory requirement, it is advisable to document business risks.
- List of potential controls as a result of identified risk(s)

Selection of potential supplier(s)

When selecting potential suppliers the manufacturer should investigate their business and operational capability, which may include technological capability, to ensure that the supplier can provide the necessary quality, safety, performance and reliability of the products and services.

Selection of potential supplier(s)

Objective evidence may include:

- The manufacturer's assessment of the supplier's resources (e.g. facilities, personnel, infrastructure), current product/service portfolio

- Documentation and records provided by the supplier, such as environmental control records, equipment maintenance programs, calibration records, qualification records of appropriate personnel, process validation records, capacity planning, certificates, etc.

Selection of potential supplier(s)

Objective evidence may include (continued):

- Documentation of potential suppliers
- Selection criteria (ideally defined up front), and
- Decision rationale

Supplier evaluation and acceptance

Generally the processes in this section are constructed in the following steps:

- Planning for evaluation and selection criteria
- Communication with potential supplier and refinement of the requirements
- Evaluation of the potential supplier's ability
- Acceptance of the supplier

Supplier evaluation and acceptance

Objective evidence for the evaluation and acceptance phase can be provided through:

- Documented evaluation and selection criteria
- Documented initial agreement(s)
- Documents and records
- Documented decision and rationale

Finalization of controls and responsibilities

The list below shows other typical areas that should be considered for finalizing the agreement between the manufacturer and its supplier.

- Complaint handling
- Root cause analysis (based on e.g. customer complaints)
- Corrective action and preventive action
- Product risk management
- Design

Finalization of controls and responsibilities

Other typical areas (continued)

- Labeling/traceability requirements
- Technical documentation (of the supply)
- Change control requirements
- Creation and retention of documents and records
- Supplier audits (including sub-tier suppliers, if appropriate)

Finalization of controls and responsibilities

Objective evidence may include:

- Contracts, purchase orders, interface agreements etc.
- Acceptance procedures; purchasing requirements
- Specifications and requirements
- Records of review and acceptance

Delivery, measurement and monitoring

In this phase the accepted supplier will deliver products/service according to the agreed arrangements and these products will be used by the manufacturer in the product realization process.

Within this process the manufacturer will establish checkpoints to monitor the supplier's performance to ensure that specifications as well as customer and regulatory requirements continue to be met.

Delivery, measurement and monitoring

Typically these activities consist of:

- Receiving product/service
- Carrying out acceptance activities
- Conducting measurement and monitoring
- Analyzing data

Objective Evidence is the records from these activities.

Feedback and communication, including Corrective Action and Preventive Action process

Provisions should be in place for the manufacturer to inform the supplier of whether the manufacturer's expectations are being met. Feedback should be both positive and negative. The manufacturer should ensure that there are effective lines of communication open to both parties to discuss problems/complaints or other matters. It is important that a relationship be developed between parties so that any problems can be resolved quickly in a cooperative way.

Feedback and communication, including Corrective Action and Preventive Action process

- When problems are identified and corrected there should be a determination as to whether feedback for a successful correction is necessary or whether feedback is given on an ongoing basis.
- If a Corrective Action or Preventive Action (CAPA) is initiated, additional feedback and communication may be necessary. As part of this action the manufacturer may need to re-evaluate the continued suitability of the supplier.

Feedback and communication, including Corrective Action and Preventive Action process

While some of the corrective action (CA) and preventive actions (PA) may be delegated to a supplier, the overall responsibility for these activities resides with the manufacturer.

CA and PA related decisions and effectiveness checks cannot be delegated!

If CA/PA activities are delegated to suppliers, the manufacturer needs to ensure that:

Feedback and communication, including Corrective Action and Preventive Action process

- Provisions for CA/PA related activities performed by suppliers are defined in the manufacturer's QMS.

- Based on the products provided by a supplier, all CA/PA specific activities to be performed and data/information to be provided by that supplier are identified (e.g. related to the extent of control necessary at the supplier).

Feedback and communication, including Corrective Action and Preventive Action process

- The supplier's obligations related to his CA/PA responsibilities are communicated to the supplier and clearly defined in a contractual agreement (e.g. in the contract itself or a quality assurance agreement).
- The supplier fulfils his contractual obligations in relation to the CA/PA activities (e.g. timely processing of corrections).
- Documentation and records related to a supplier's CA/PA activities are controlled and readily available.

Feedback and communication, including Corrective Action and Preventive Action process

Objective evidence may include:

- Manufacturer and/or supplier correspondence
- Documentation and records of corrective action and preventive action process

Introduction to Global Harmonization Task Force Study Group 4 Regulatory Auditing

5th APEC-Funded Seminar on Harmonization of Medical Device Regulations

Speakers

Albert T.W. Li
Manger and Senior Administrator
Office of Medical Device Evaluation
Industrial Technology Research Institute
Chinese Taipei

Armand Tsai
Quality Systems Officer
Medical Devices Bureau
Health Canada

Overview

- Introduction to SG4
  - Membership
  - Role of Study Group 4
  - Regulatory Programmes
  - External Influences
- SG4 Guidance Documents

Membership

- Unites States
  - 2 regulatory

  (Chair: Ms. Jan Welch, FDA)
  - 1 industry
- Canada
  - 1 regulatory
  - 1 industry
- Australia
  - 1 regulatory
- European Union
  - 2 regulatory
  - 3 industry
  - 2 Notified Body
- Japan
  - 2 regulatory
  - 1 industry
- Taiwan
  - 1 regulatory (AHWP liaison)

Role of Study Group 4

SG4 has been charged with the task of examining quality system auditing practices* and developing guidance documents laying harmonized principles for the medical device auditing process.

* - initially among the founding members of the GHTF

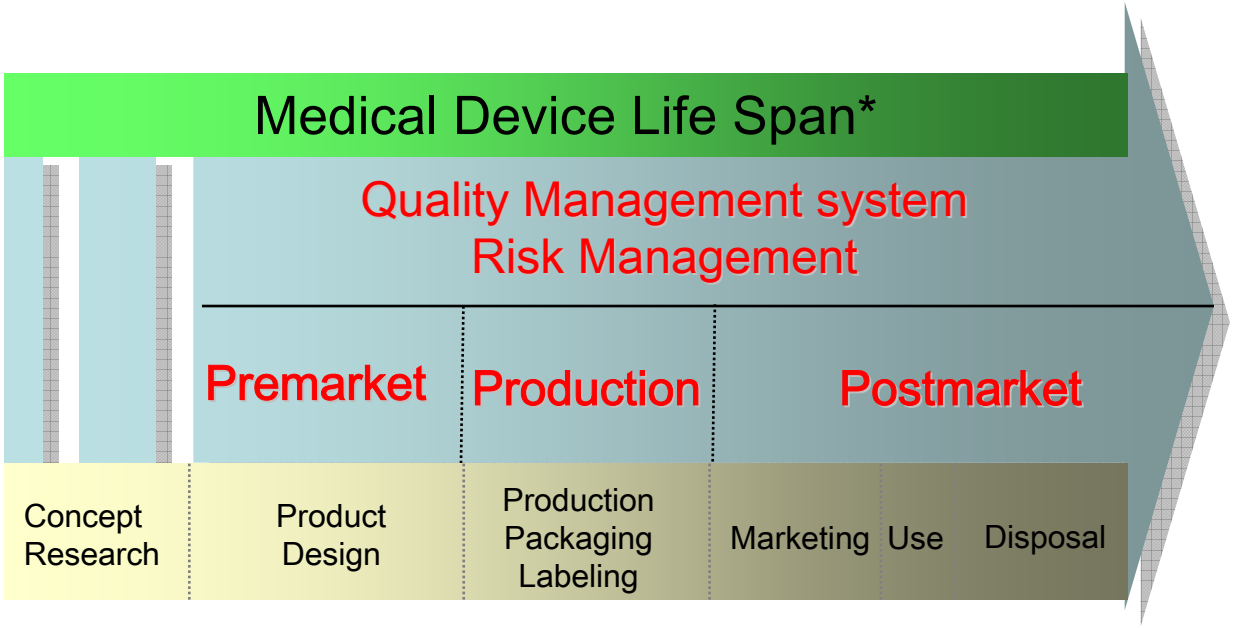
Role of Study Group 4

The goals of this Study Group include:

- Improving the effectiveness of regulatory audits
- Promoting greater uniformity in the way regulatory bodies throughout the world conduct audits

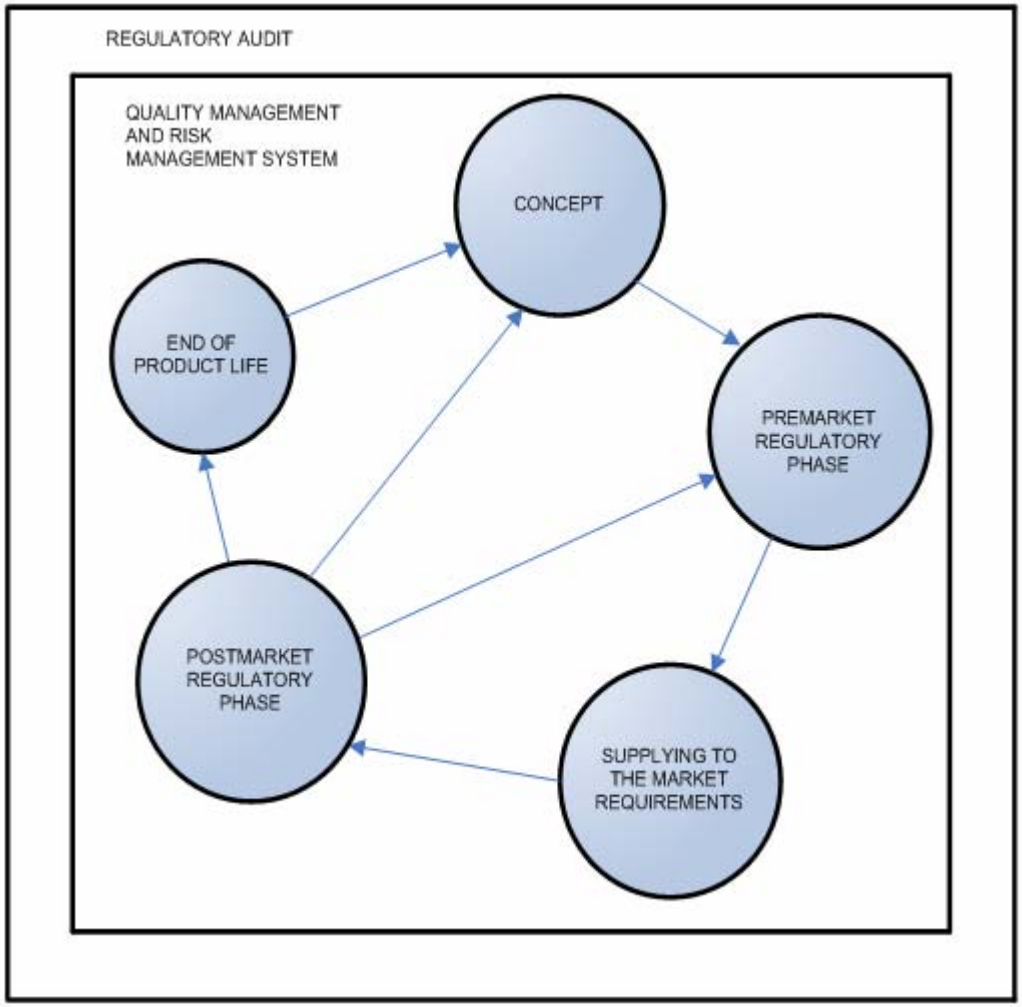
Role of Study Group 4

- Regulatory auditing covers all aspects of the life-cycle of a medical device.



*: World Health Organization: Medical Device Regulations, 2003

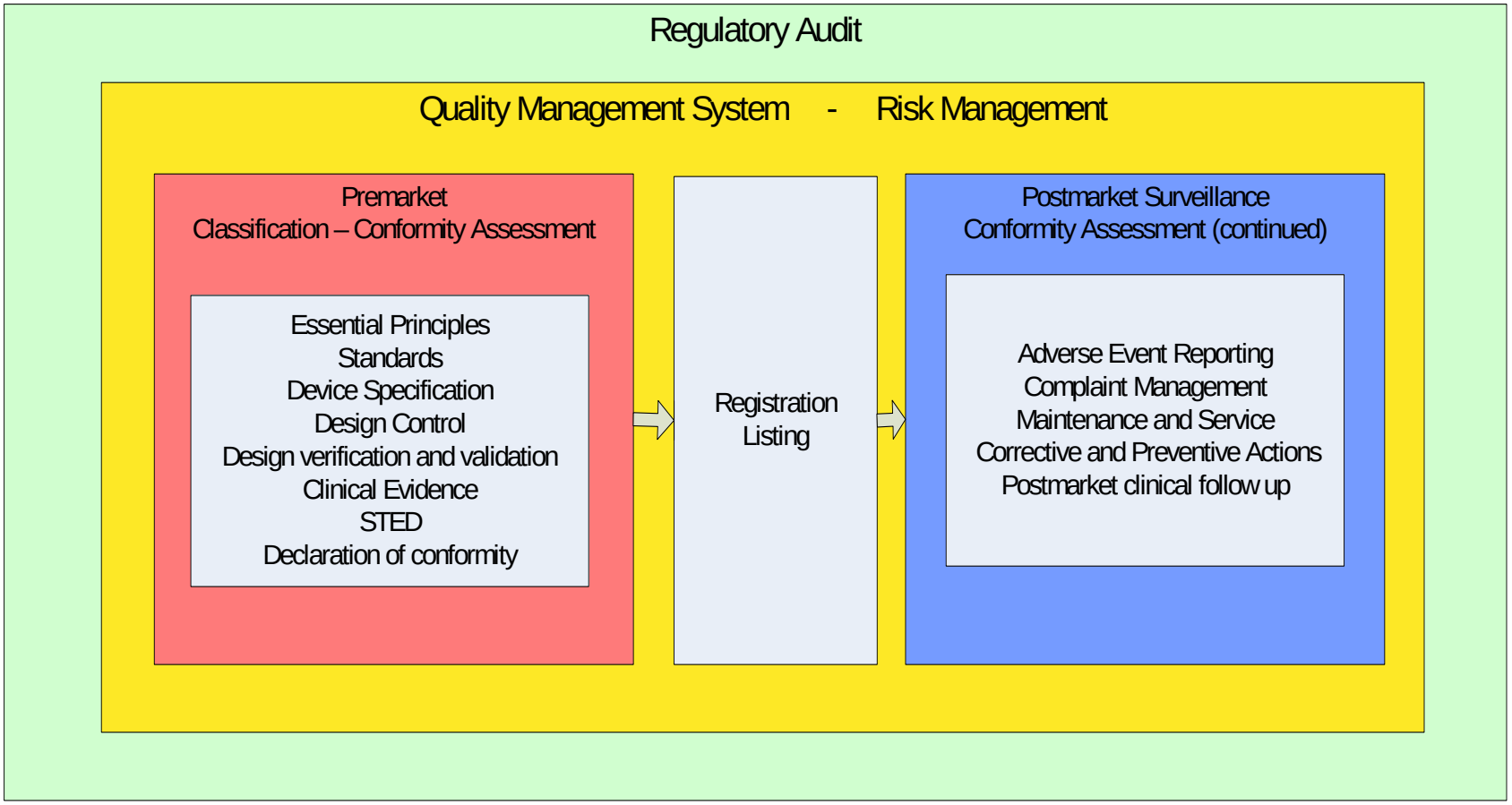
Role of Study Group 4



Role of Study Group 4

- Within the GHTF Medical Device Regulation Model, regulatory auditing spans the entire model, from the start of the product lifecycle to its end.

Role of Study Group 4



Regulatory Programmes

- The founding members of GHTF use a variety of programmes for their medical device regulatory audits.
- Some of theses are highly centralised while others are more distributed.

Regulatory Programmes

	US	Australia	Japan	EU	Canada
Regulatory Body	Food & Drug Administration (FDA)	Therapeutic Goods Administration (TGA)	Ministry of Health, Labour and Welfare (MHLW)	Competent Authorities (CA)	Health Canada (HC)
QMS standard	21 CFR Part 820 based on ISO 13485:1996	ISO 13485:2003	Ordinance 169-2004 based on ISO 13485:2003	EN ISO 13485:2003	ISO 13485:2003
QMS verification	FDA + QS/GMP Inspection AP	TGA	MHLW + 3rd party in some cases	Notified Body (NB) (3rd party)	Registrar (3rd party)
Pre-market review	FDA + 510(k) Review AP	TGA	MHLW + PMDA	NB (3rd party)	HC
Post-market compliance & enforcement	FDA	TGA	MHLW	CA + NB (3rd party)	HC

Regulatory Programmes

- The guidance prepared by SG4 can be used in centralized programmes (US, Australia, Japan) as guidance on the operation of a regulatory agency, or in decentralized programmes (Canada, EU) as evaluation criteria for third-party conformity assessment bodies.

External Influences

The work of SG4 is influenced by:

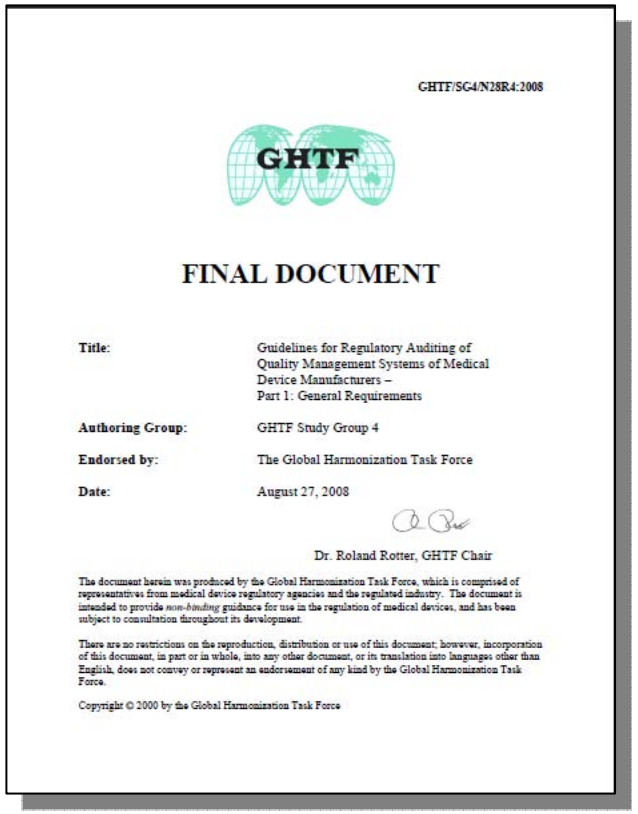
- The regulatory framework of the founding members of the GHTF;
- The work of ISO CASCO;
- The work of ISO TC176 & TC210; and,
- To a lesser extent, the guidance issued by the International Accreditation Forum (IAF).

SG4 Guidance

- Provide guidance for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers
  - SG4 N28 Part 1: General requirements
  - SG4 N30 Part 2: Regulatory auditing strategy
  - SG4 N33 Part 3: Regulatory audit reports
  - SG4 N83 Part 4: Multiple site auditing (draft)
  - SG4 N84 Part 5: Audits of supplier controls (draft)
  - SG4 (00) 3 Training Requirements for Auditors (Supplement 2)

GHTF/SG4/N28R4: 2008
Part 1 General Requirements

- Endorsed by GHTF in 1999
- Revised in 2008
  - Revised structure
  - Reference to pertinent sections of relevant standards such as ISO 19011: 2002, ISO 17000:2004, and ISO 17021: 2006
  - Elimination of duplicate information
  - Updated with current terminology and practice



GHTF/SG4/N28R4:2008

GHTF

FINAL DOCUMENT

Title:	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 1: General Requirements
Authoring Group:	GHTF Study Group 4
Endorsed by:	The Global Harmonization Task Force
Date:	August 27, 2008

Dr. Roland Rotter, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, which is comprised of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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SG4/N28R4: 2008
Part 1 General Requirements

- Provides guidance to regulators and auditing organizations conducting audits of quality management systems (QMS) of medical device manufacturers based on the process approach to QMS requirements (e.g., ISO 13485 and 21 CFR 820)
- Provides the opportunity for developing mechanisms that would lead to global harmonization by incorporating QMS requirements into applicable regulations.

SG4/N28R4: 2008
Part 1 General Requirements

- Provides guidance for auditing organizations responsible for establishing, planning, carrying out, and documenting audits of medical device manufacturers' QMS.
- Covers related requirements on the follow-up of corrections, corrective, preventive, or improvement actions.
- Describes the competence criteria of the audit team.

General Requirements for Auditing Organizations

- Legal responsibility
- Independence and impartiality
- Confidentiality, due professional care and code of ethics
- Liability and financing

Management and Resources

- Management
  - Structural requirements
  - Quality management system
  - Consistency
- Resources
  - Competent staff, financial support, time to conduct effective audits, and access to technical information and external expertise
  - May not outsource decisions with respect to certification

Types of Audits

- Full audit
  - All applicable subsystems of QMS, initial audit
- Partial audit
  - Some subsystems or aspects of subsystems of QMS, surveillance audit or special audit

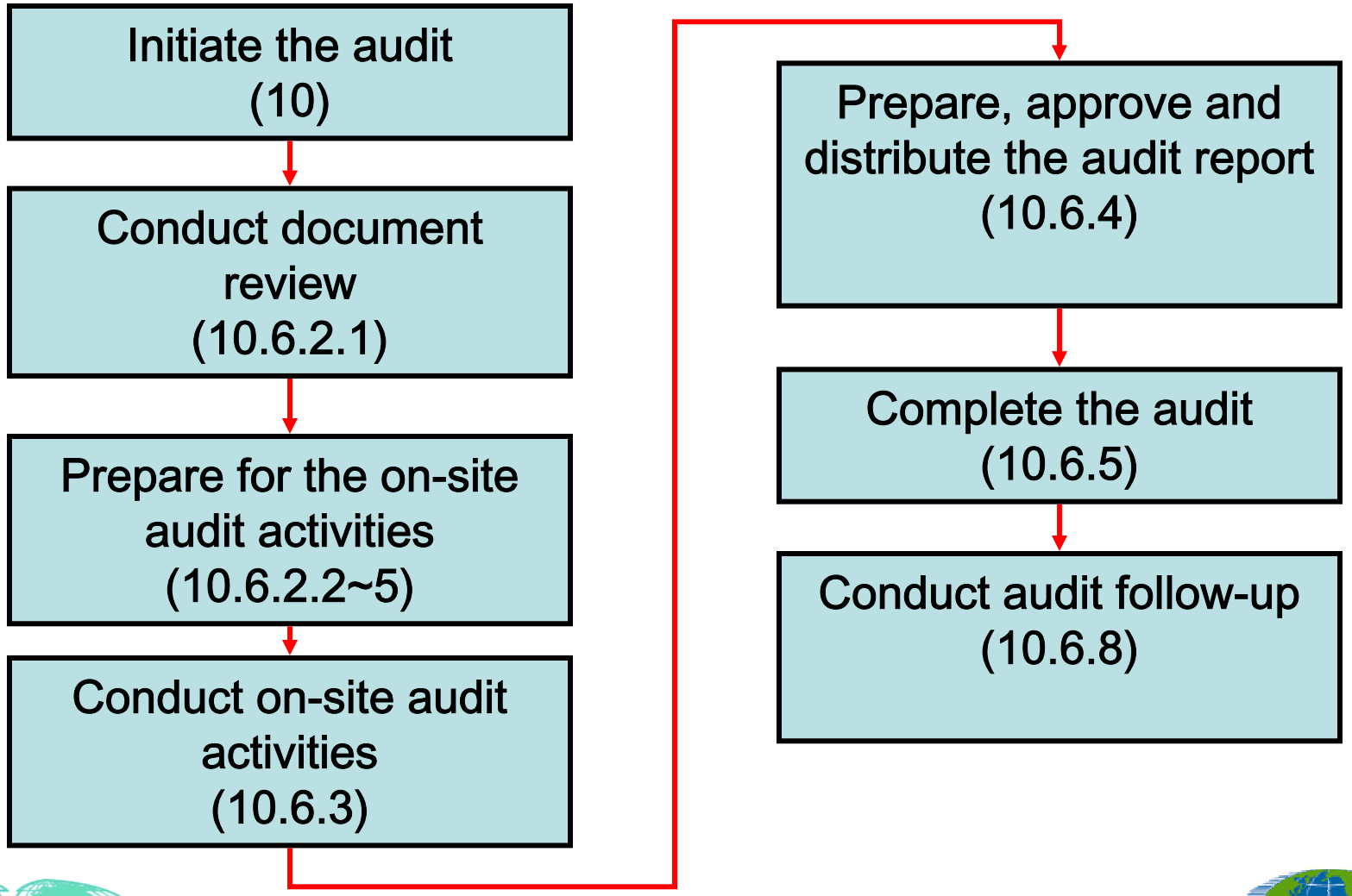
Types of Audits

- Surveillance audit
  - After the initial audit, partial audit
  - Annual frequency, no greater than 3 years or 2 years (high risk devices)
- Special audit
  - Full or partial audit
  - Postmarket surveillance, significant product safety
  - Significant changes of QMS, product, standards and/or regulation
- Combined audit
  - Multiple regulatory purposes
- Joint audit
  - Two or more auditing organizations audit an auditee against the same regulatory requirements at the same time

Roles, Responsibilities and Authorities

- Ensure a clear understanding of mutual expectations throughout the audit process
- Provide a means of accountability with respect to relevant requirements
  - Auditing organization
  - Auditor
  - Lead auditor
  - Auditee
  - Observers
  - Language

Audit Process



Nonconformities

- Are written in a clear, concise manner
- Are supported by objective evidence
- Identify the specific requirements which have not been met
- Are identified as a major or minor nonconformity

Major Nonconformities

- Failure to address or implement applicable regulatory requirements for QMS
- An excessive number of minor nonconformities
- Failure to implement appropriate corrective and preventive action (CAPA) for known or potential product defects
- Undue risk of products
- Product does not comply with specifications or requirements
- Repeated nonconformities from previous audits

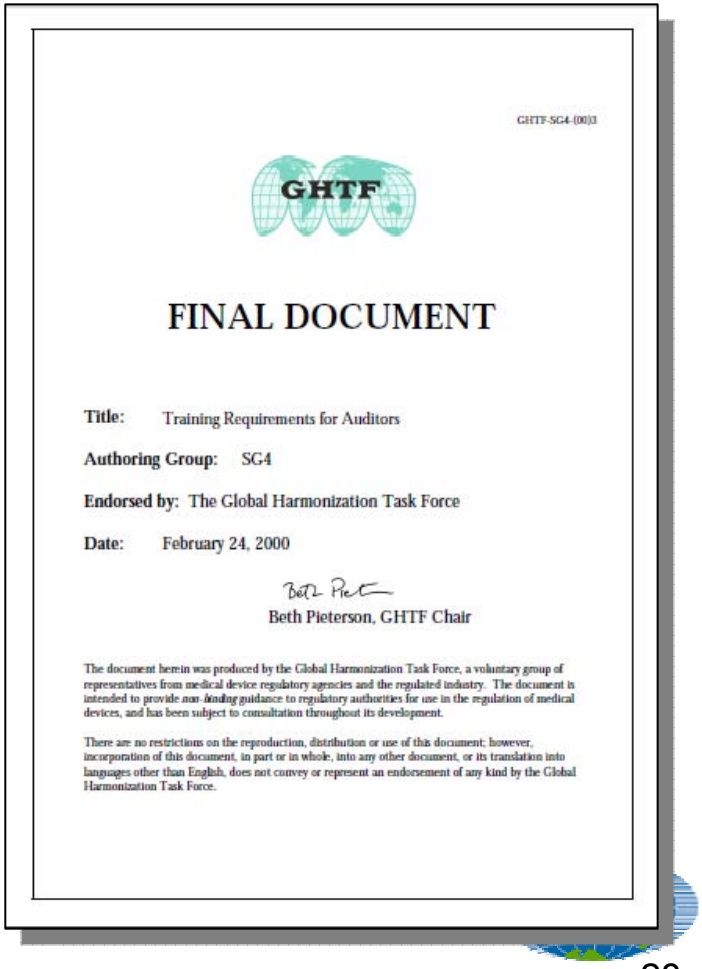
Follow-up Activities

- CAPA are decided and undertaken by the manufacturer and/or auditee within an agreed upon timeframe
- CAPA is not part of the audit
- The status of CAPA should be monitored by the manufacturer and/or auditee
- The auditing organization should review and verify the completion of CAPA. The verification may be part of a subsequent audit

GHTF-SG4-(00)3
Part 1 General Requirements Supplement 2
Training Requirements for Auditors

This document offers guidance on how to:

- Prepare an individual to be an auditor
- Qualify auditors to conduct regulatory audits of medical device manufacturers' quality systems
- Maintain auditors' qualifications
  - Training program
  - On-the-job training
  - Continuous professional development
  - Advanced training elements of auditors
  - Auditor qualification



GHTF-SG4-(00)3

GHTF

FINAL DOCUMENT

Title: Training Requirements for Auditors

Authoring Group: SG4

Endorsed by: The Global Harmonization Task Force

Date: February 24, 2000

Beth Pieterson, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. 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.

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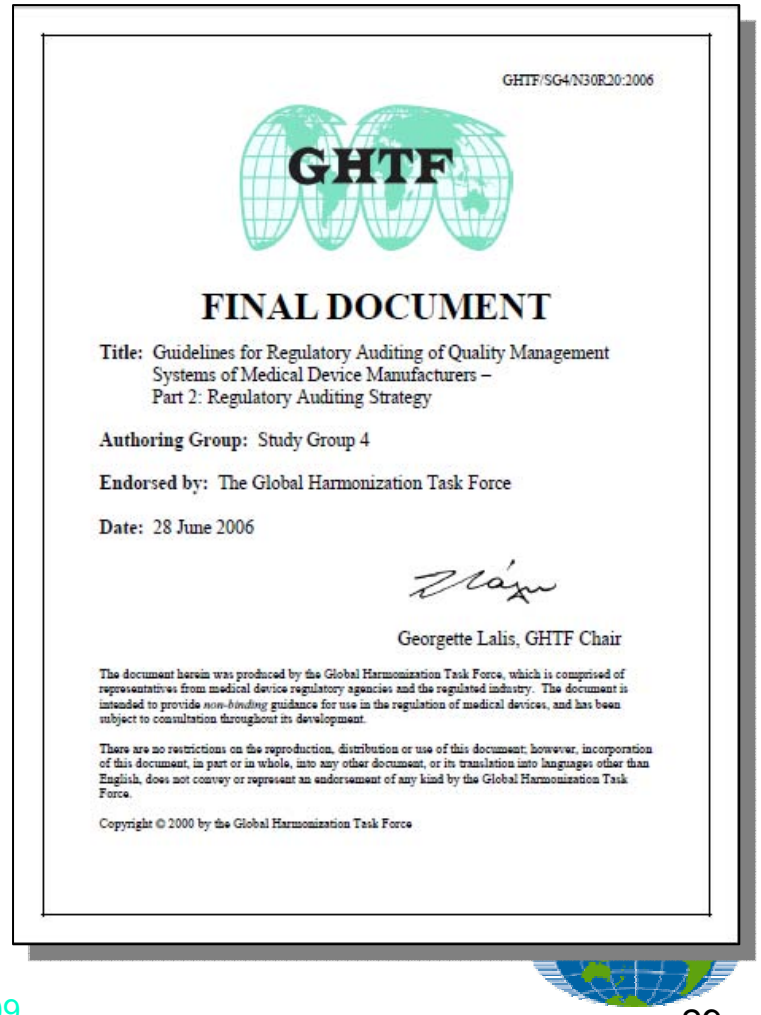
GHTF

GHTF/SG4/N30R20:2006
Part 2: Regulatory Auditing Strategy

- This guideline is intended to be used by regulators and auditing organizations conducting QMS audits of medical device manufacturers based on the process approach to QMS requirements (e.g., ISO 13485:2003 and 21 CFR Part 820).
- This guideline applies to initial and surveillance audit
- It aims to promote consistency in conducting audits – a necessity for harmonization and mutual recognition of audit results



GHTF/SG4/N30R20:2006

GHTF

FINAL DOCUMENT

Title: Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy

Authoring Group: Study Group 4

Endorsed by: The Global Harmonization Task Force

Date: 28 June 2006

Georgette Lalis, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, which is comprised of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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GHTF/SG4/N30R20:2006
Part 2: Regulatory Auditing Strategy

- The audit should be process-oriented and should preferably follow the workflow processes of the medical device manufacturer.
- The audit should be risk-based with a focus on key QMS processes necessary to manufacture the medical devices covered by the audit.
- The auditor should concentrate on factors that are most likely to affect safety of the medical devices while at the same time ensuring adequate coverage of all classes of medical devices within the scope of the audit.

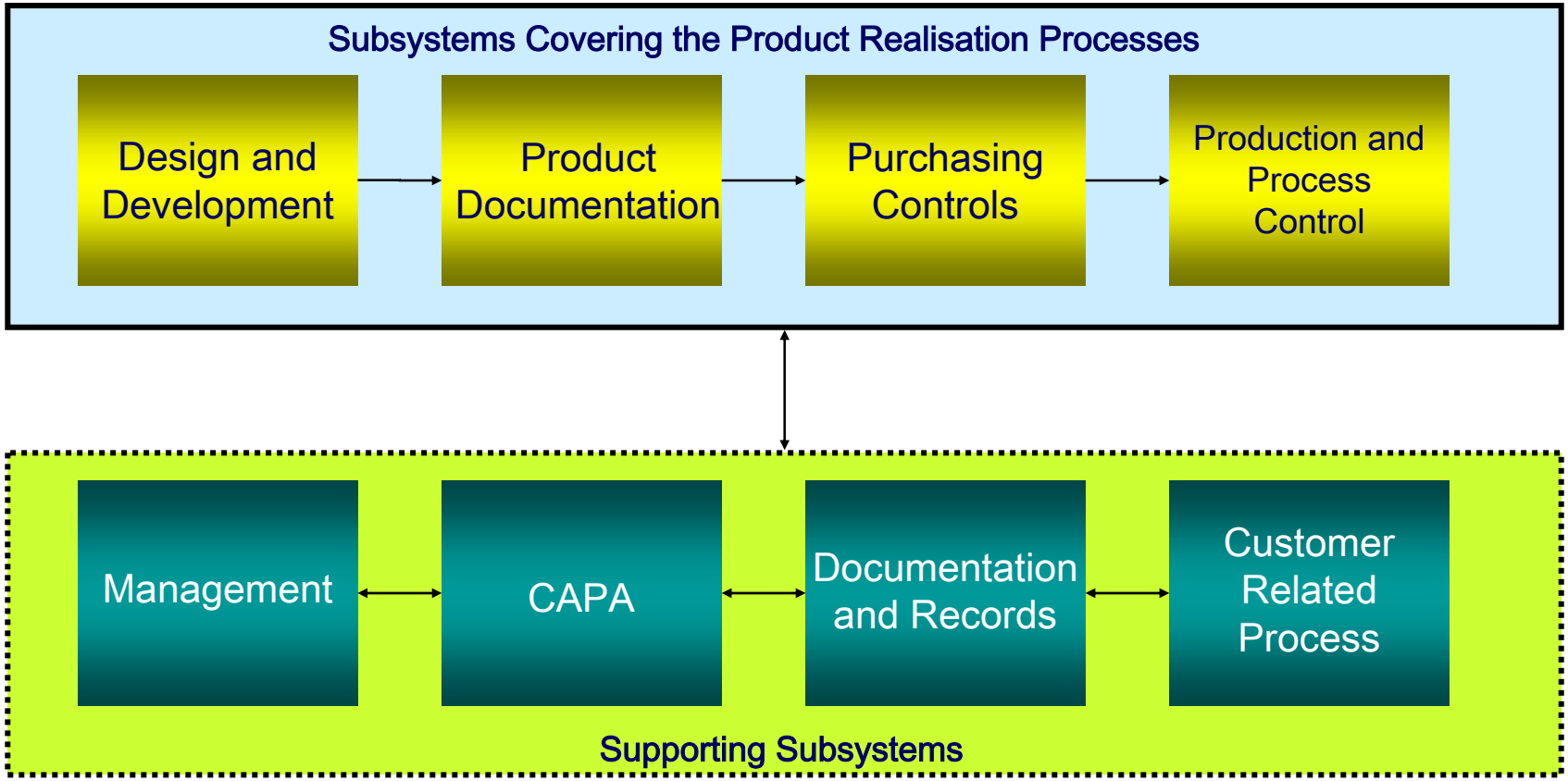
Objectives of A Regulatory Audit

- The effectiveness of the manufacturer's QMS – including the fulfillment of regulatory requirements - is assessed in a systematic and effective manner within a reasonable time period.
- The results of the audit are consistent regardless of which auditing organization or individual auditors conduct the audit. The ultimate goal is for harmonization and mutual recognition of audit results.
- The audit determines how problems associated with a medical device or the QMS are recognized and addressed.
- The audit is transparent to the auditee.

Auditing Subsystems

Subsystems	Clauses and subclauses (links) of ISO 13485:2003
1. Management	4 QMS, 5 Management responsibility, 6 Resource management, 7 Product realization, 8 Measurement, analysis and improvement
2. Design and development	7 Product realization,
3. Product documentation	4 QMS, 7 Product realization
4. Production and process controls (including sterilization, where applicable)	4 QMS, 6 Resource management, 7 Product realization, 8 Measurement, analysis and improvement
5. Corrective and preventive actions	4 QMS, 5 Management responsibility, 6 Resource management, 7 Product realization, 8 Measurement, analysis and improvement
6. Purchasing controls	7 Product realization,
7. Documentation and records	4 QMS
8. Customer related processes	7 Product realization,

Subsystem Links



Auditing Approaches

- **The "top-down" approach:** Begins with an evaluation of the structure of the QMS
- **The "bottom-up" approach:** Starts at the bottom such as with a quality problem
- **The "combination" approach:** Starts by reviewing the top layer of the QMS then audits aspects of the implementation of the systems
- **The "product" approach:** Selects a single medical device, batch, or lot and follows its history

Audit Planning

- Information required from the manufacturer
- Estimation of audit duration, frequency and target on-site auditing time

Subsystems	*Approximate percentage ofon-site time*	*Remarks*
1. Management	*5-10 %*	
2. Design and development	*0-20%*	*Depends on regulatory requirements*
3. Product documentation	*5-20%*	
4. Production and process controls (including sterilization, where applicable)	*20-30 %*	
5. Corrective and preventive actions	*10-30 %*	
6. Purchasing controls	*5-20%*	*Depending on the proportion and importance of activities an outsourcing manufacturer is contracting*
7. Documentation and records	*5 %*	
8. Customer related processes	*5 %*	

Auditing Subsystems

- Risk management principles apply throughout the product realisation process of a medical device and should be used to identify and address safety issues.
- Risk management activities should be audited concurrently with the relevant subsystems. (see *GHTF-SG3/N15 R8: 2005 Implementation of Risk Management Principles and Activities within a Quality Management System*.)
- The purpose of auditing the risk management process is to ensure that adequate and effective risk management has been established and maintained throughout the product realization process.

Management Subsystem

- Verify that a quality manual, management review and quality audit procedures, quality plan, and QMS procedures and instructions have been defined and documented.
- Verify that a quality policy and objectives have been defined and documented and steps taken to achieve them.
- Verify that the product realisation 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 (cont'd)

- Review the manufacturer's organizational structure and related documents to verify that they include provisions for responsibilities, authorities (e.g., management representative), resources, competencies and training.
- Verify that management reviews are being conducted and that they include a review of the suitability and effectiveness of the QMS.
- Verify that internal audits of the QMS are being conducted and that they include verification of CAPA.
- The audit commences and ends with the management subsystem, however between the opening and closing of management subsystem the other subsystems are audited.

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).
- Review documents describing the design process and select sufficient records to cover the manufacturer's product range. Focus on individual products rather than families.
- Criteria for selection:
  - product risk
  - complaints or known problems
  - age of design (prefer most recent)
- Review the design plan for the selected product(s) to understand the design and development activities, including assigned responsibilities and interfaces.

Design and Development Subsystem (cont'd)

- For the product design record(s) selected, verify that design and development procedures have been established and applied.
- Verify that design inputs were established and address customer functional, performance and safety requirements, intended use, applicable regulatory requirements, and other requirements essential for design and development.
- Review medical device specifications to confirm that design and development outputs meet design input requirements. Verify that the design outputs essential for the proper functioning of the medical device have been identified.

Design and Development Subsystem (cont'd)

- 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
- Verify that design validation data show that the approved design meets the requirements for the specified application or intended use(s).
- Verify that clinical evaluations and/or evaluation of the medical device safety and performance were performed if required by national or regional regulations.
- If the medical device includes software, verify that the software was part of the medical device's design and development validation.

Design and Development Subsystem (cont'd)

- Verify that design changes were controlled and verified or, where appropriate validated, and that design changes have been addressed.
- Verify that design reviews were conducted.
- Verify that design changes have been reviewed for the effect on products previously made and delivered, and that records of review results are maintained.
- Determine if the design was correctly transferred to production.

Product Documentation Subsystem

- Verify if there are documents needed by the organization to ensure planning, operation and control of its processes.
- Select product documentation for sufficient product(s) to cover the manufacturer's product range
- For the product(s) selected verify that documentation includes (if required by national or regional regulations):
  - evidence of conformity to requirements, including standards used
  - medical device description including instruction for use, materials and specification
  - summary of design verification and validation documents including clinical evidence
  - labelling
  - risk management documents
  - manufacturing information including major suppliers

Production and Process Controls Subsystem

- Verify that the product realization processes are planned – including any necessary controls and controlled conditions.
- Verify that the planning of product realization is consistent with the requirements of the other processes of the QMS.
- Review production processes considering the following criteria. Select one or more production processes to audit.
  - CAPA indicators of process problems
  - Use of production process for higher risk products
  - New production processes or new technologies
  - Use of the process in manufacturing multiple products
  - Processes not covered during previous audits

Production and Process Controls Subsystem (cont'd)

- Verify that the processes have been validated if the result of the process cannot be verified. Verify that the validation demonstrates the ability of the processes to achieve planned result.
- Verify that the equipment used in production and process control has been adjusted, calibrated and maintained.

Production and Process Controls Subsystem (cont'd)

- Verify that the processes are controlled and monitored and operating within specified limits. In addition, 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.
- Determine the links to other processes.
- Verify that personnel are appropriately qualified and/or trained to implement/maintain the processes.
- Verify that the infrastructure and the work environment are adequate.
- Verify that identification and traceability for processes and products are in place and are adequate.

Production and Process Controls Subsystem (cont'd)

- If the process is software controlled, verify that the software is validated for its intended use.
- Verify that the control of the monitoring and measuring devices is adequate.
- Verify that the system for monitoring and measuring of products is adequate. Ensure that any identified risk control measures are implemented.
- Verify that acceptance activities assure conformance with specifications and are documented.
- Verify that the control of nonconforming products is adequate.

Corrective and Preventive Actions – CAPA Subsystem

- Verify that CAPA system procedure(s) which address the requirements of the QMS have been established.
- Verify that accurate information is analysed for input into the CAPA system and that CAPA were effective.
- When a CAPA results in a design change, verify that the hazard(s) and any new risks are evaluated under the risk management process.
- Determine if all appropriate sources of CAPA data have been identified and are being monitored to determine action when indicated. Confirm that data from these sources are analyzed, using valid statistical methods where appropriate, to identify existing product and quality problems that may require corrective action.

Corrective and Preventive Actions – CAPA Subsystem (cont'd)

- Determine if failure investigations are conducted to identify the causes of nonconformities, where possible.
- Verify that controls are in place to prevent distribution of nonconforming products.
- Confirm that CAPA were implemented, effective, documented and did not adversely affect finished devices.
- Determine if relevant information regarding nonconforming product and quality problem(s) and CAPA has been supplied to management for management review.

Corrective and Preventive Actions – CAPA Subsystem (cont'd)

- Verify that medical device reporting is done according to the applicable regulatory requirements.
- Confirm that the manufacturer has made effective arrangements for gaining experience from the post production phase, handling complaints and investigating the cause of non-conformance related to advisory notices/recalls with provision for feed back into the CAPA subsystem.
- Confirm that the manufacturer has made effective arrangements for the issue and implementation of advisory notices/recalls.

Purchasing Controls Subsystem

- Verify that procedures for conducting supplier evaluations have been established.
- Verify that the manufacturer evaluates and maintains effective controls over suppliers, so that specified requirements are met.
- 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.
- Verify that records of supplier evaluations are maintained.
- Determine that the verification of purchased products and services is adequate.

Documentation and Records Subsystem

- Verify that procedures have been established for the identification, storage, protection, retrieval, retention time and disposition of documents and records. (Including change control).
- Confirm that documents and changes are approved prior to use.
- Confirm that current documents are available where they are used and that obsolete documents are no longer in use.
- Verify that required documents and records are being retained for the required length of time.

Customer Related Processes Subsystem

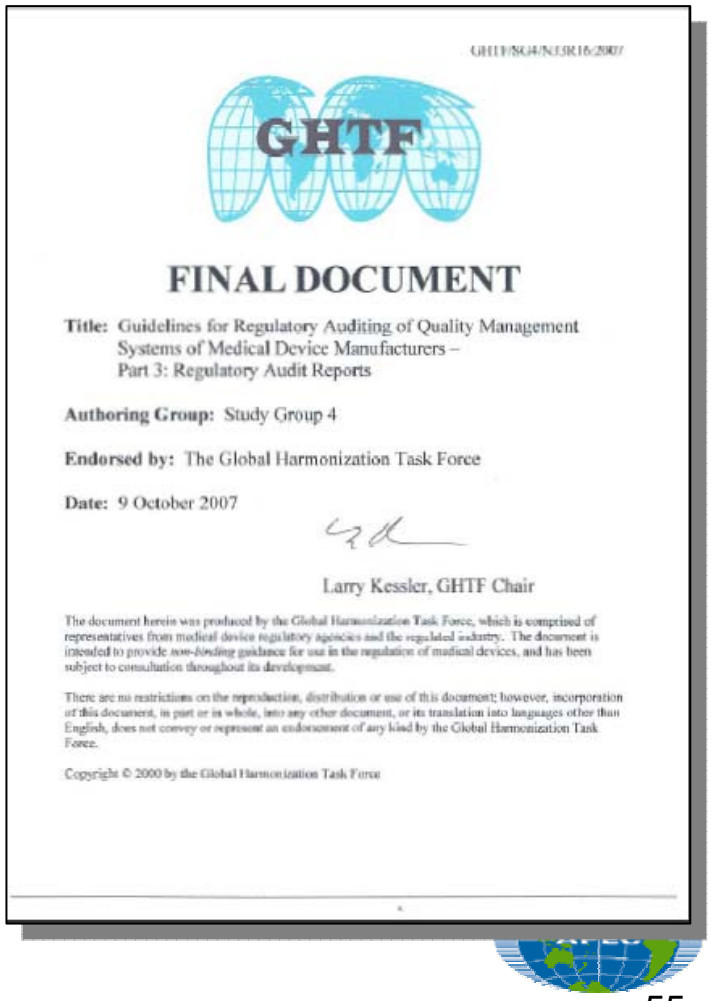
- Review product requirements to verify that they address the intended use as well as customer and regulatory requirements.
- Confirm that incoming orders and related information are reviewed to assure that any conflicting information is resolved and the manufacturer can fulfil the customer's requirements.
- Confirm that the manufacturer has made effective arrangements for handling communications with customers including documenting customer feedback to identify quality problems and provide input into the CAPA 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.

Appendix

- Appendix 1: Binominal Staged Sampling Plans
- Appendix 2: Factors Used to Determine Audit Duration
- Appendix 3: Cross-reference between ISO 13485:2003 and 21 CFR Part 820
- Appendix 4: Sterilization Process

SG4/N33 R16
Part 3: Regulatory Audit Report

- This document is intended to be used by regulators and auditing organizations as a guide for writing a report of a regulatory medical device QMS audit.
- This guideline describes a report which can be exchanged with other regulatory or auditing organizations with which the auditing organization has a formal relationship concerning confidentiality
- The purposes of this document are to harmonize the content of audit reports and to provide guidance on best practices for reporting audit results.



GHTF/SG4/N33R16:2007

GHTF

FINAL DOCUMENT

Title: Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports

Authoring Group: Study Group 4

Endorsed by: The Global Harmonization Task Force

Date: 9 October 2007

Larry Kessler, GHTF Chair

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This Guideline Aims to

- Harmonize the content of audit reports
- Provide guidance on best practices for reporting audit results.
- Provide a structure for audit reports that may be used in multiple jurisdictions
- Promote consistency and uniformity and assist the auditor in preparing a report for use by multiple regulators and/or auditing organizations.
- Have reports that are consistent in content to facilitate the review and exchange of audit reports.
- Eventually reduce the number of audits for manufacturers through the acceptance of audit reports by multiple regulators.

Audit Report Objectives

- The audit report comprises the documented evidence of a regulatory audit.
- It should contain sufficient information:
  - To document the audit scope, type of audit, audit objectives, the audit criteria, what was covered during the audit, and the audit findings
  - To evaluate the auditee's compliance status, the effectiveness of the implementation of the QMS, and draw audit conclusions
  - To allow the exchange of audit reports between regulators and/or auditing organizations

The Main Points of a Regulatory Audit Report

- Data concerning auditee
- Data concerning audit
- Audit trail
- Conclusion
- Signature and dating of report
- Attachments

Draft Documents

- SG4(PD)/N83 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 4: Multiple Site Auditing
- SG4(PD)/N84 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 5: Audits of Supplier Controls

Thank you very much!

You can visit us online at the GHTF website

Inquiries about the work of SG4 can be directed to the Chair:

Ms. Jan Welch
Food and Drug Administration
Center for Devices and Radiological Health
2094 Gaither Road , HFZ-320
Rockville , MD 20850
UNITED STATES
Tel: 1-240-276-0354
Fax: 1-240-276-0114
e-mail: jan.welch@fda.hhs.gov

Case Study: Management Representative

- 3 different companies have appointed people in the following positions as management representatives:
  1. Vice President – Sales
  2. Vice President – Quality Assurance/Regulatory Affairs
  3. Vice President - Production
- What questions or concerns, if any, do you have about each appointment?

Case Study: Component Change

- Superior Devices, Inc., just developed a specification for a new component for an existing device, using design controls. The change is necessary because there have been failures involving this component.
- What other documents, procedures, etc. might be affected by the changed specification?

Changes to other documents?

- Design history file
- Device Master Record
- Device specifications
- Component specifications
- Purchasing documents
- Incoming inspection/test procedure
- Assembly procedure
- In-process inspection/test procedure
- Finished device inspection/test procedure
- Installation/servicing procedure

Case Study: Component Change

- Superior Devices, Inc., is purchasing the same component from a new supplier because the old supplier is now out of business. The effective date of the change is “when the stock of old components has been used up.”
- Is the effective “date” acceptable? Why or why not?
- What if the component change was being made because the component was redesigned to address component failures that led to device failures?

Case Study: Testing Later Rather Than Sooner

- Perfect Devices does not test in-process electronic assemblies because testing is time-consuming and expensive. Instead they conduct extensive finished device testing, which enables them to identify defective assemblies and replace them.
- Is Perfect Devices violating the Acceptance Activity requirements because they do not test in-process assemblies?
- Why or why not?

Case Study: Models for Manufacturing

- Certain devices at Superior Devices, Inc., are assembled by hand. Many employees do not speak or read the local language. To help employees understand how to assemble the devices, models showing the components, the order of assembly and the finished assemblies are at each work station.
- When assembly procedures or components are changed, how should changes for the models be handled?

Case Study: Personnel Requirements

- During an audit of Superior Devices, auditor Sleuth noticed a work station in the clean room with a box of tissue and a wastebasket filled with crumpled tissues.
- If you were auditor Sleuth what would you want to check into further regarding this situation?

Case Study: Process Validation

- During an audit Sarah Sleuth reviewed the validation of a wave soldering process for a new device. There was no documentation of installation qualification for the wave soldering machine. When she raised this with the company, they told her they have been using a wave soldering machine for 5 years without problems and that should be adequate qualification of the wave soldering machine.
- Is 5 years of use an adequate installation qualification? Why or why not?

Case Study: CAPA

- Sixteen customers have returned electronic monitors to OK Devices because the monitors did not work when they were taken out of the box and plugged in. OK immediately shipped replacement monitors to the customers with a note of apology, documented this action and closed the CAPA on this incident for the CAPA system.
- Has OK taken an adequate action? Explain why or why not.
- What should auditor Sleuth do?

Case Study: Complaint Handling

- Perfect Devices, Inc. has received 10 complaints alleging that their device sparked several times before ceasing to function. PD investigated the first 3 complaints and identified the root cause of the problem. They are working on a redesign to eliminate the problem. They have not investigated the 7 remaining complaints.
- Is not investigating the 7 remaining complaints acceptable? Why or why not?

Case Study: Complaint Handling

- Regarding the previous case study, Perfect Devices, Inc. identified the cause of sparking and failure to function after investigating 3 of 10 complaints, Mary Jones, who reviewed the complaints, documented the reason for not investigating 7 of the complaints with the statement: “Similar to complaints #XXX, XXY, and XXZ for which cause was identified. CAPA initiated 3/8/05.”
- Is this acceptable? Why or why not?

Case Study: Purchasing Controls

- Perfect Devices, Inc. (PD) just found out their supplier of injection molded polystyrene plastic components is going out of business. They need a new supplier quickly. Two years ago they purchased latex components from Raja Rubber, Inc. Raja Rubber also makes injection molded polystyrene components.
- Can PD rely on their previous supplier evaluation of Raja Rubber, or should they perform a new evaluation?
- Explain your answer.

Case Study: Maintaining Records

- Sleep Tite, Inc, makes hospital beds. During an audit, auditor Sarah Sleuth finds that Sleep Tite has destroyed all required records over 5 years old.
- Should auditor Sleuth write a non conformity for failure to maintain records for the required length of time?
- What else do you need to know about this situation?