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

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

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

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

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

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

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

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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**

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Determination of acceptable levels of risk:

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

Risk analysis:

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

Determination of risk reduction measures:

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

Risk control and monitoring activities:

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

Risk control and monitoring activities:

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

Risk control and monitoring activities:

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

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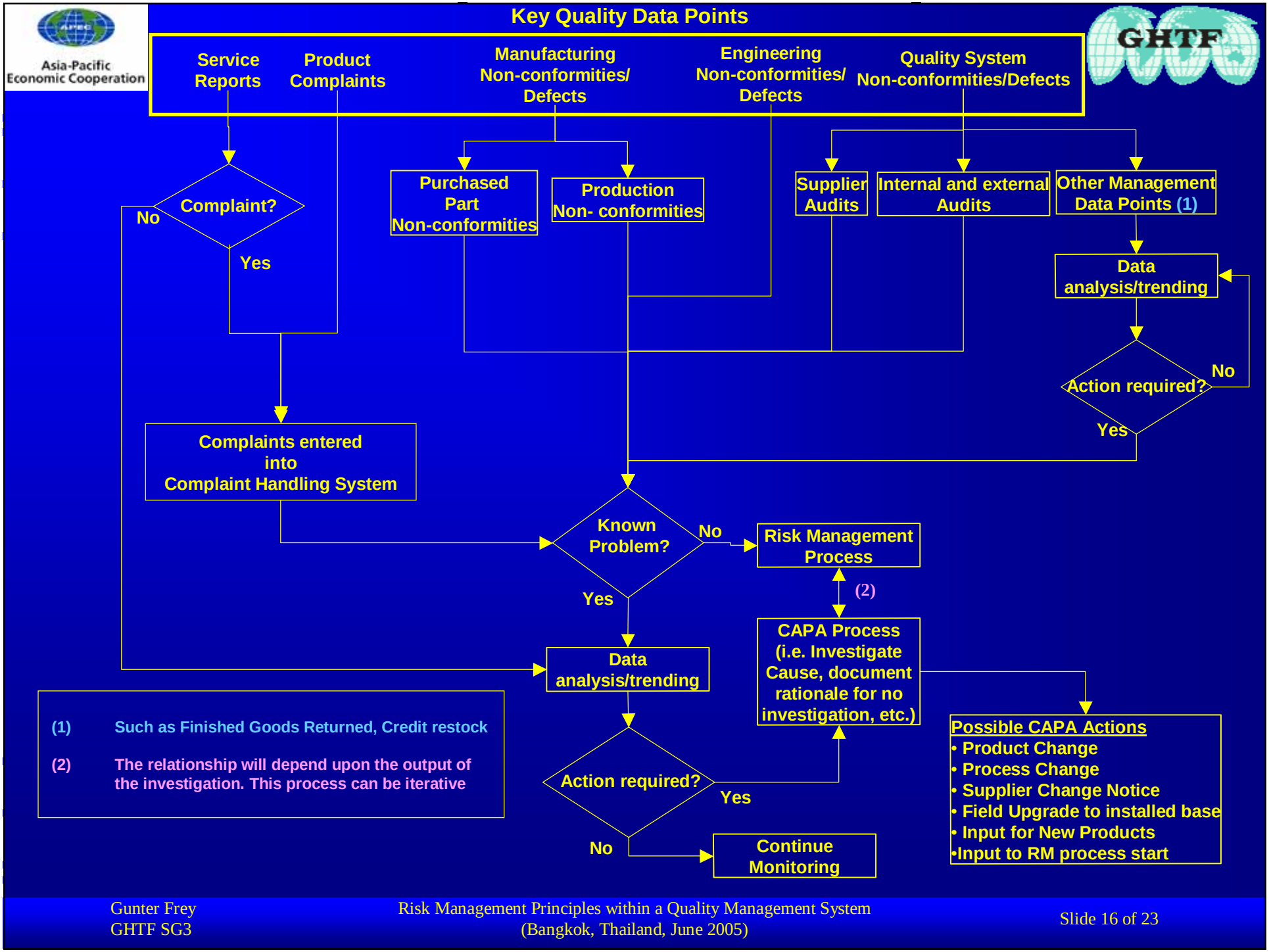
Risk control and monitoring activities:

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

Let's examine this a little closer …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Key Quality Data Points
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Service Reports
Product Complaints
Manufacturing Non-conformities/ Defects
Engineering Non-conformities/ Defects
Quality System Non-conformities/Defects
Complaint?
No
Yes
Purchased Part Non-conformities
Production Non- conformities
Supplier Audits
Internal and external Audits
Other Management Data Points (1)
Data analysis/trending
Action required?
No
Yes
Complaints entered into Complaint Handling System
Known Problem?
No
Yes
Risk Management Process
(2)
CAPA Process (i.e. Investigate Cause, document rationale for no investigation, etc.)
Possible CAPA Actions
• Product Change
• Process Change
• Supplier Change Notice
• Field Upgrade to installed base
• Input for New Products
•Input to RM process start
Data analysis/trending
Action required?
Yes
No
Continue Monitoring
(1) Such as Finished Goods Returned, Credit restock
(2) The relationship will depend upon the output of the investigation. This process can be iterative

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Risk control and monitoring activities:

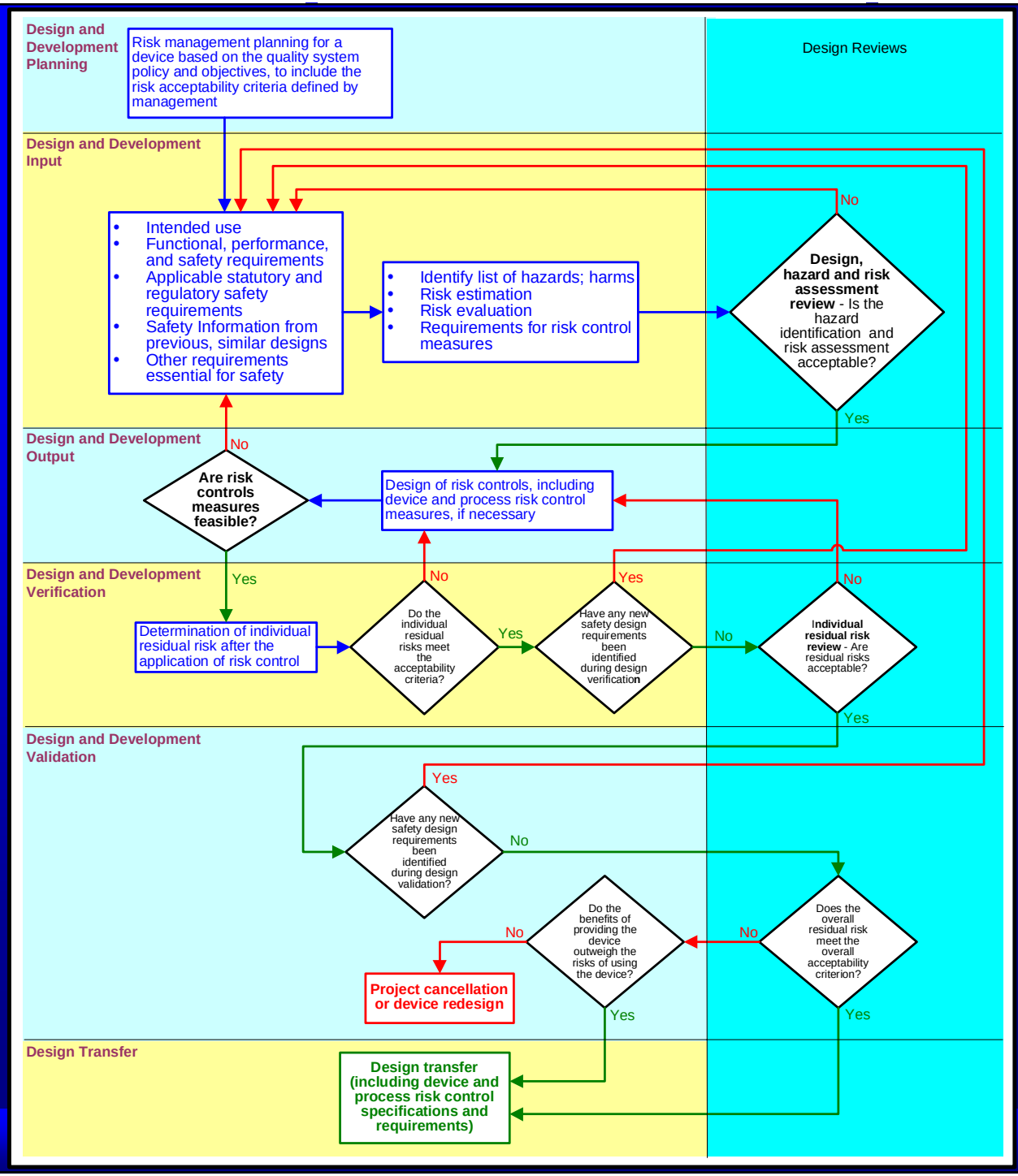
- If, at any time, a risk is determined to be unacceptable, part or all of the existing risk analysis should be re-examined and appropriate action taken to meet the established risk acceptability criteria.
- If a new hazard is identified, all four phases of risk management should be performed.

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 its acceptability as a part of the completed design validation


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

Risk Management In The Quality System

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

Risk Management In The Quality System

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

Risk Management Principles and Activities Within a Quality Management System

Case Study

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Temporomandibular Joint (TMJ) Implants

Temporomandibular Joint (TMJ)

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

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

The socket (fossa) is part of the skull.

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

TMJ Implants

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

Both products included Teflon as key components.

TMJ Implants

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

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

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

TMJ Implants

Patients and physicians began reporting problems, including:

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

TMJ Implants

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

TMJ Implants

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

As discussed in previous slides….

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

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

Determination of acceptable levels of risk:

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

Risk analysis

Known and published general hazards were not properly recognized

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

Risk estimation

Overall activity appears to have been incomplete!

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

For example:

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

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Determination of risk reduction measures:

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

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

Risk control and monitoring activities

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

1988 – product distribution suspended

1990 – Company issues advisory letter to physicians

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This is a case where risk management:

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

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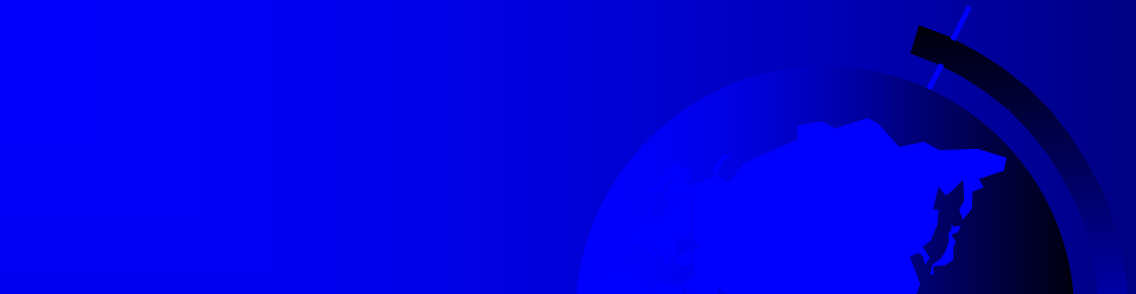
Thank you on behalf of Study Group 3 and the GHTF for your time and attention.

Questions?

APPENDIX



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Definitions

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

Definitions

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

Definitions

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

Regulatory Links & Sources of Standards

Additional information

European Medical Device Directive 93/42/EEC:
http://3.70.4.1/~qualsys/regulatory/MDD/1993L0042_consolid.pdf

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

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

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

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

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

China:

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

Additional information (cont.):

FDA:

General:
http://www.fda.gov

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

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

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

Note: While Directives amending 93/42/EEC have been published (specifically Directive 98/79/EC
Directive 2000/70/EEC, and Directive 2001/104/EEC), GE Healthcare Technologies does not currently manufacture products governed by these directives – GE Healthcare BioSciences might.

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/