GHTF SG4
APEC 2005

AUDITING

June 13-17, 2005

Asia-Pacific
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Overview of the Global Harmonization Task Force (GHTF)

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Trainers

Larry Spears

Center for Devices & Radiological Health

U.S. Food and Drug Administration

Tim Missios

Canadian Industry (MEDEC) Representative

Boston Scientific Corporation

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GHTF

Introduction

- Brief History/Goal
- Steering Committee
- FIVE (5) STUDY GROUPS (SGs)
- SG4 Auditing

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Brief History/Goal

- Established 1992
- USA, EC, JA, AU, & CA
- International Partnership
- Harmonize Regulatory Practices

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GHTF Goals

"The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness / performance and quality of medical devices, promoting technological innovation and facilitating international trade, and the primary way in which this is accomplished is via the publication and dissemination of harmonized guidance documents on basic regulatory practices. These documents, which are developed by five (5) different GHTF Study Groups, can then be adopted/implemented by member national regulatory authorities."

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Benefits of GHTF

"The GHTF also serves as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with existing systems and/or pattern their practices upon those of GHTF founding members."

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GHTF MEMBERSHIP Represents:

- Regulatory authorities
- Industry

From the five founding countries

–Australia - Canada

–European Union - Japan

–United States of America

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GHTF Structure

- Steering Committee:
  - regulatory and industry members from each founding geographic area
- Study Groups
  - 5 study groups

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Steering Committee

- Provides Policy Direction
- Strategic Planning
- Assign & Provide Oversight Of Technical Work Initiatives
- Decision on SG Actions

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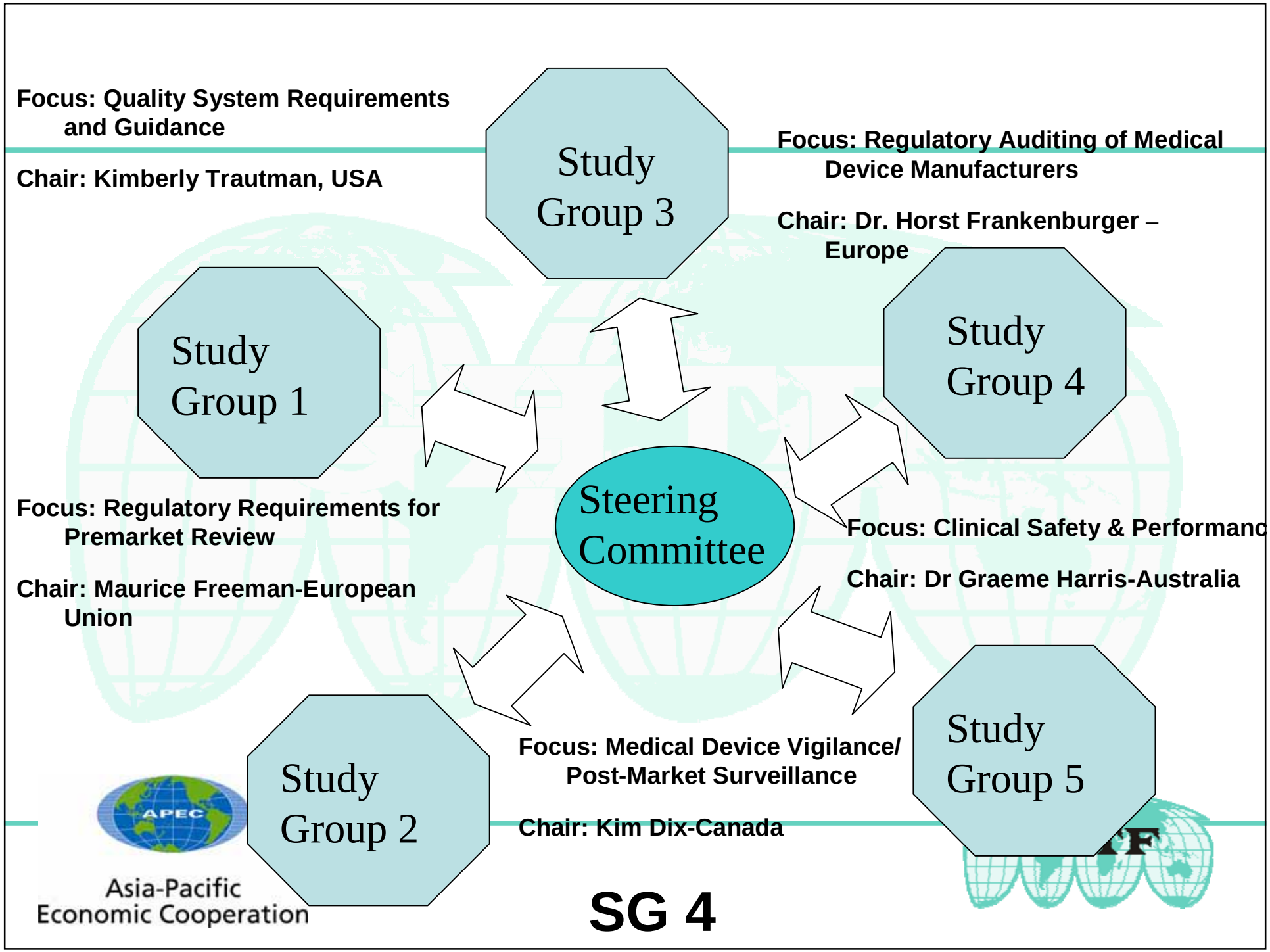
Focus: Quality System Requirements and Guidance
Chair: Kimberly Trautman, USA
Study Group 3
Focus: Regulatory Auditing of Medical Device Manufacturers
Chair: Dr. Horst Frankenburger – Europe
Study Group 1
Study Group 4
Steering Committee
Focus: Regulatory Requirements for Premarket Review
Chair: Maurice Freeman-European Union
Focus: Clinical Safety & Performanc
Chair: Dr Graeme Harris-Australia
Study Group 2
Focus: Medical Device Vigilance/ Post-Market Surveillance
Chair: Kim Dix-Canada
Study Group 5
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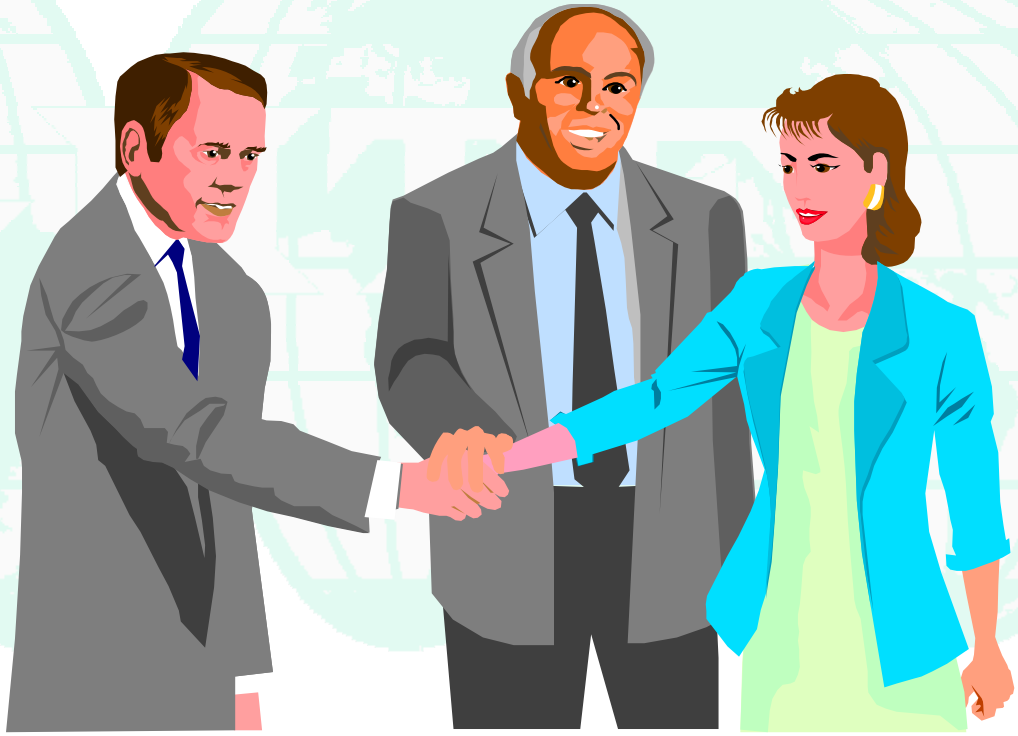
- GHTF welcomes observers from other countries!



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How to Participate in GHTF

- Check GHTF web site for new guidance documents
- Comment on proposed guidance
- Adopt final guidance documents as appropriate
- Attend GHTF conferences

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Additional Information on GHTF

Visit the GHTF web site at: www.ghtf.org

Website includes:

- Steering Committee & procedures documents
- Study group guidance documents & membership
- Discussions from past GHTF conferences
- Upcoming Meetings and strategic plan 2005-2007

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Global Harmonization Task Force
Study Group 4 – Auditing

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Agenda

- Goals of SG 4 – Auditing
- SG 4 Membership
- Definitions of terms
- Summary of guidance documents

GHTF SG 4 “Auditing” - Purpose

Purpose of Study Group SG4

- **Guidance to Regulatory Audit Organizations, Auditors and Manufacturers of Medical Devices**

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

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Goals of GHTF SG 4

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

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SG 4 Current Membership

- **U.S. (3)**
  - Regulatory (2)
  - Industry (1)
- **Canada (2)**
  - Regulatory (1)
  - Industry (1)
- **Australia (1)**
  - Regulatory (1)
- **Europe (6)**
  - Regulatory (1)
  - Industry (3 – **SG4 Chair & Secretary**)
  - EU Notified Bodies (2)
- **Japan (4)**
  - Regulatory (2)
  - Industry (2)

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SG 4 – Five Final Guidance Documents

Guidelines for

Regulatory Auditing

of Quality Management Systems of Medical Device Manufacturers - Part 1- General Requirements

Four Supplements to document

GHTF.SG4.(99)28

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SG 4 – Five Final Guidance Documents

SG4(99)14, Supplement 1:
Audit Language Requirements

SG4(00)3, Supplement 3:
Training Requirements for Auditors

SG4-N(99) 24 R3, Supplement 4:
Compilation of Audit Documentation

SG4 N26 R1,Supplement No. 6
Observed Audits of Conformity Assessment Bodies

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Document not revised yet for the new era
ISO 13485:2003

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SG 4 – One Proposed Guidance Document

SG4/N30 R 13:

Guidelines for

Regulatory Auditing

of Quality Management Systems of

Medical Device Manufacturers

Part 2: Regulatory Auditing Strategy

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SG 4 – Guidance Documents Under Development

SG4/N33: Part 3: Audit Reports

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SG 4 Final Guidance

GHTF.SG4.(99)28: Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 1- General Requirements

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SG 4 – Main Guidance Document

- Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers: General Requirements
- Contains general principles and guidance for managing and conducting regulatory audits
- Other guidance documents supplement it

Part 1: General Requirements

- Scope:
  - Guidelines for auditing organisations
  - Competence criteria for the *audit* team
  - Requirements for the *audit* report and follow-up on corrective actions

General Requirements:

Definitions

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Audit

- A systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives [ISO 8402]

More . . .

Audit cont'd

- For the purpose of these guidelines, *"audit"* means *audit* of the *auditee's quality system* to determine compliance with the relevant *regulatory requirements*

Auditee

- Any organisation whose quality systems are to be *audited* for compliance with the relevant medical device *regulatory requirements*
- *Note. This can be the manufacturer and/or their subcontractor(s)*

Auditing Organization

- A body designated, on the basis of specific regulations, to carry out *audits* according to assigned tasks

Auditor

- A person with relevant qualifications and competence to perform *audits* or specified parts of such *audits* and who belongs to, or is authorised by, the *auditing organisation*

Manufacturer

- The legal entity subject by regulation to *quality system* requirements
- *Note 8. In several international standards the term 'supplier' is substituted for the term 'manufacturer'*

Nonconformity

- The non-fulfilment of specified requirements within the planned arrangements
- Other terms with the same meaning as *nonconformity* are “non-compliance” and “deficiency”

Quality System

- The organisational structure, responsibilities, procedures, processes and resources for implementing quality management [ISO 8402].
- For the purpose of these guidelines 'implementing quality management' is taken to include both the establishment and maintenance of the system

Regulatory Requirements

- For the purpose of these Guidelines any part of a law, ordinance, decree or other regulation which applies to *quality systems* of medical device manufacturers

General Requirements:

Important Principles for Regulatory Auditing

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Independence of Auditors

- *Auditing organisations* and *auditors* shall be impartial and free from engagements and influences which could affect their objectivity

Independence of Auditors

- *Auditing organisations* and *auditors* shall not be:
  - Involved in design, construction, marketing, installation, servicing or supply of devices being audited
  - Involved in design, construction, implementation or maintenance of *quality system* being audited
  - An authorised representative of the *manufacturer*

Responsibility for Quality System

- *Audits* do not result in a transfer of the responsibility for implementing an effective *quality system* from the *manufacturer* to the *auditing organisation*

More . . .

Responsibility for Quality System

- The *manufacturer* is ultimately responsible for implementing and maintaining an effective *quality system* and taking necessary corrective and preventive actions

General Requirements:

Other Elements of Managing the Audit Process

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Audit Objectives and Scope

- Should be:
  - Clearly defined and documented by the *auditing organisation* and the *audit* team
  - Agreed to by the *manufacturer,* as permitted by *regulatory requirements*
- May be modified, based on the quality *audit* observations

Types of Audits

- Initial *audit*
- Surveillance *audit*
- Special *audit*
- Unannounced *audit*

Initial Audit

- First *audit* of *manufacturer*
- All elements of *quality system* should be audited

Surveillance Audit

- *Manufacturer* has been audited previously
- *Audit* may cover complete *quality system* or only part of it

Surveillance Audit

- Interval between surveillance audits is determined by:
  - Risk associated with intended use of the medical devices
  - Number of *quality system* elements to be examined
  - Nature of *quality system* elements to be examined
  - Scope and results of previous *audits*
  - Any post market surveillance data indicating a possible deficiency in *quality system*

Special audit

- An *audit* conducted when:
  - Post-market surveillance data indicate a possible significant deficiency in the *quality system*
  - Significant safety related information is obtained from another source
  - Significant changes occur to a *manufacturer*, which could affect the decision on the *manufacturer*'s state of compliance with the *regulatory requirements*

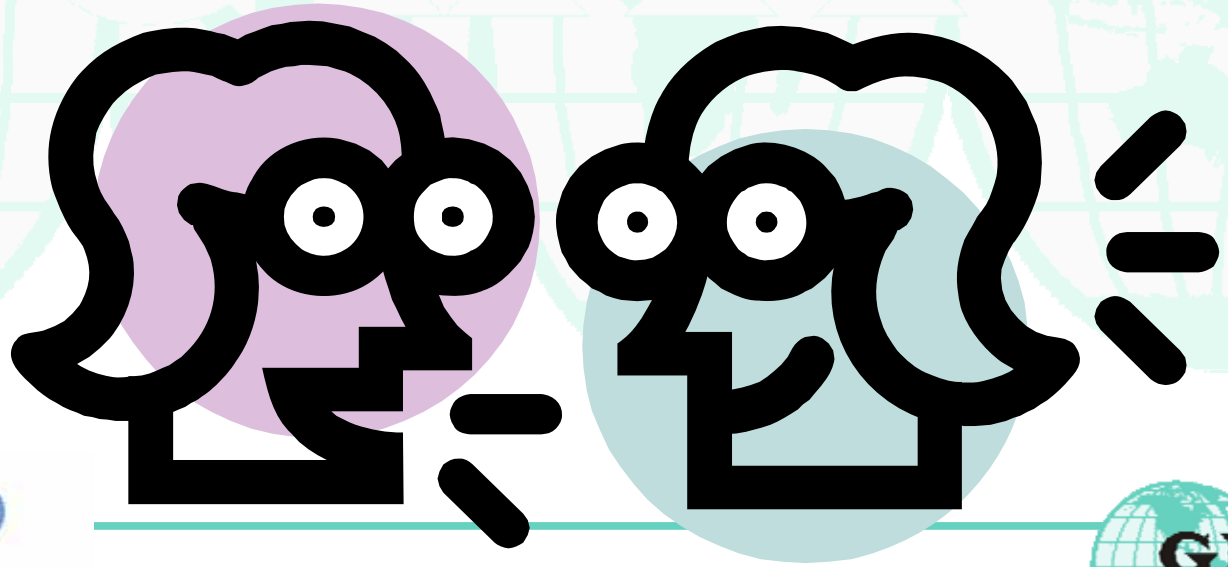
Unannounced Audit

- An unannounced *audit* may be conducted when the *auditing organization* has justifiable concerns about the *manufacturer's* implementation of corrective actions or compliance with *regulatory requirements*

SG 4 Final Guidance

SG4(99)14, Supplement 1:

Audit Language Requirements



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Audit Language Requirements

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

SG 4 Final Guidance

SG4(00)3, Supplement 3:
Training Requirements for Auditors

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Training Requirements for Auditors

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

Training Topics to Prepare an Individual to Be an Auditor

1. Principles and applications of quality systems and auditing
2. Interviewing people
3. Collecting, documenting and reporting quality audit observations and non-conformities
4. Auditing organization's policies and procedures

Training Topics to Qualify Auditors to Conduct Regulatory Audits

1. Understanding, applying and enforcing laws and *regulatory requirements*
2. The role of the *auditing organization*
3. Principles and applications of *quality systems* and auditing for medical device *manufacturers*

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Training Topics to Qualify Auditors to Conduct Regulatory Audits

4. Overview of medical devices, their intended uses, safety and risks

5. Overview of processes commonly used to design and manufacture medical devices

Training Topics to Qualify Auditors to Conduct Regulatory Audits

6. Special training on specific topics such as sterilization processes and in–vitro diagnostics

7. On–the-job or practical training in conducting *audits*

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Training to maintain auditor qualifications

1. Training courses
2. Scientific meetings
3. Independent study

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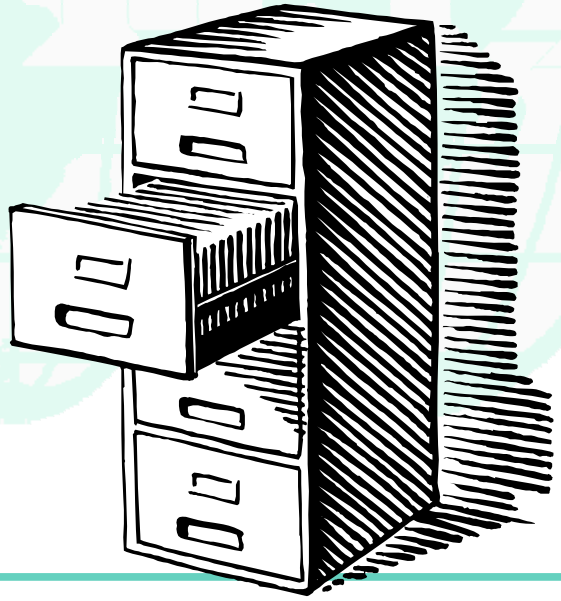
Assuring that Auditors are Qualified

- Experienced *auditor* should observe and evaluate *auditor*-in-training conducting one or more audits
- *Auditors* should be judged competent to conduct *audits* before they are allowed to work without supervision
- *Auditors* should be judged competent to *audit* highly specialised technologies before they are allowed to work without supervision

SG 4 Final Guidance

SG4-N(99) 24 R3, Supplement 4: Compilation of Audit Documentation



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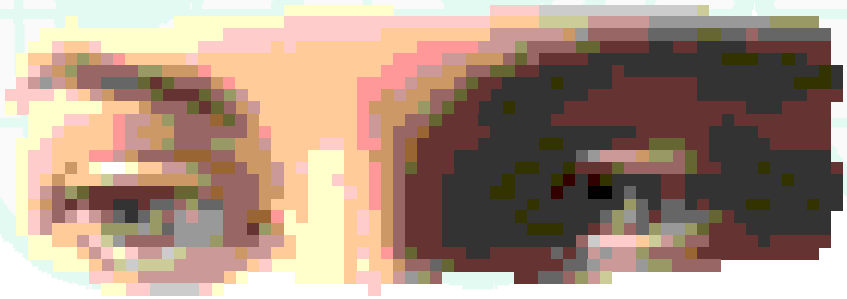
Compilation of Audit Documentation

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

SG 4 Final Guidance

SG4 N26 R1,Supplement No. 6
Observed Audits of Conformity Assessment Bodies



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Observed Audits of Conformity Assessment Bodies

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

Remember:

- To audit = to listen
  > need to understand language!
- Only trained auditors will do a good job!
- No job is finished until the paperwork is done!

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Benefits by applying the principles stated in document GHTF.SG4.(99)28

- Common understanding how to audit manufacturer <> auditing organisation
- Alignment of procedures between auditing organisations
- Improvement of audit quality

SG 4 Proposed Guidance

SG4/N30 R 13:
Guidelines for
Regulatory Auditing
of Quality Management Systems of
Medical Device Manufacturers
Part 2: Regulatory Auditing Strategy
First Draft to GHTF-Steering Committee: March 2003

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Regulatory Auditing:

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Auditing Strategy

- **Purpose:** to provide guidance on how to audit quality systems for conformance with regulatory requirements
- Having a consistent approach for auditing that GHTF members agree upon can encourage members to rely on one another's audits
- Promote audit consistency – a necessity for harmonization and mutual recognition of audit results.

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Auditing Strategy

- Introduction, Scope, References, & Definitions
- General Remarks
- Auditing Sub-systems
- Appendices

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Scope

- ISO 13485:2003 & 21 CFR 820
- Risk Management
- Software, Human Factors
- Additional Regulatory Requirements
- Initial & Surveillance Audits

References

- GHTF/SG4/N28R2
- GHTF/SG1/011R16
- 21 CFR 820
- QSIT
- 21 CFR 803, 806, & 821
- ISO 13485:2003
- ISO 19011:2002
- ISO/TC 210/WG1 N62
- ISO/IEC GUIDE 62:1996 & APPLIC.
- ISO 14971:2000
- GHTF SG3/N99-8
- GHTF SG3/N99-9
- GHTF SG3/N99-10
- GHTF SG3/N15 R6

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Definitions

- Audit
- Regulatory Audit
- Audit Criteria
- Audit Evidence
- Technical Files
- Medical Device
- Process
- Regulatory Requirements
- Establish
- Risk Mgt

General Remarks

- Objectives
- Systems & Sub-systems
- Audit Approaches
- Process Based Auditing
- Sampling
- Planning - Audit Frequency and Duration
- Logistics
- Linkages

Objectives of a Regulatory Audit

- The effectiveness of the manufacturer‘s quality system is to measure and to monitor in a systematic and effective manner within a reasonable time
- Process-orientation of the audit – according to ISO 13485:2003
- Audit with a focus on key processes
- Transparency of the audit to the auditee
- Similiarity of the audit process and results – regardless of which audit organization and individual auditors conduct the audit

Auditing Sub-systems

- Subsystems have been identified – associated with clauses of ISO 13485:2003 and sections of 21 CFR Part 820
- Subsystems based in part on the **Q**uality **S**ystem **I**nspection **T**echnique (QSIT): Management, Design and development, Production processes, Corrective and preventive actions
- GHTF SG4 has identified additional subsystems: Technical files, Purchasing controls, Documentation and records, Customer requirements

Auditing sub-systems

- Management
- Design and development
- Technical files
- Production processes
- Corrective and preventive actions
- Purchasing controls
- Documentation and records
- Customer requirements

Auditing sub-systems (cont'd)

Management

GOAL: The purpose of the management subsystem audit is to evaluate whether top management ensures that an adequate and effective quality system has been established and maintained.

Auditing sub-systems (cont'd)

Design and Development

GOAL: The purpose of auditing the design and development subsystem is to determine whether the design process is controlled to ensure that devices meet user needs, intended uses and specified requirements.

Auditing sub-systems (cont'd)

Technical Files

GOAL: The purpose of auditing the technical files is to confirm that the manufacturer has taken the necessary steps to ensure that products will be safe and effective.

Auditing sub-systems (cont'd)

Production Processes

GOAL: The purpose of auditing the production process (including testing, infrastructure, facilities and equipment) is to confirm that the production process is able to ensure that the products will meet specifications.

Auditing sub-systems (cont'd)

Corrective and Preventive Actions – CAPA

GOAL: The purpose of auditing the CAPA subsystem (including reporting / tracking) is to confirm that information is collected and analyzed to identify actual and potential product and quality problems, that these are investigated, and appropriate and effective corrective and preventive actions are taken.

Auditing sub-systems (cont'd)

Purchasing Control

GOAL: The purpose of auditing the purchasing control activities is to ensure that products, components, materials and services supplied by suppliers, (including contractors and consultants) are in conformity. This is particularly important when the finished product or service cannot be verified by inspection (e.g. sterilisation services).

This subsystem should be considered a main subsystem for "virtual manufacturers".

Auditing sub-systems (cont'd)

Documentation and Records

GOAL: The purpose of auditing the documentation and records is to ensure that the relevant documents are controlled within the manufacturer, and critical subcontractors covered by the scope of this audit, and that the relevant records are available.

Auditing sub-systems (cont'd)

Customer Requirements

GOAL: The purpose of auditing customer requirements is to ensure that customer requirements including regulatory requirements are met.

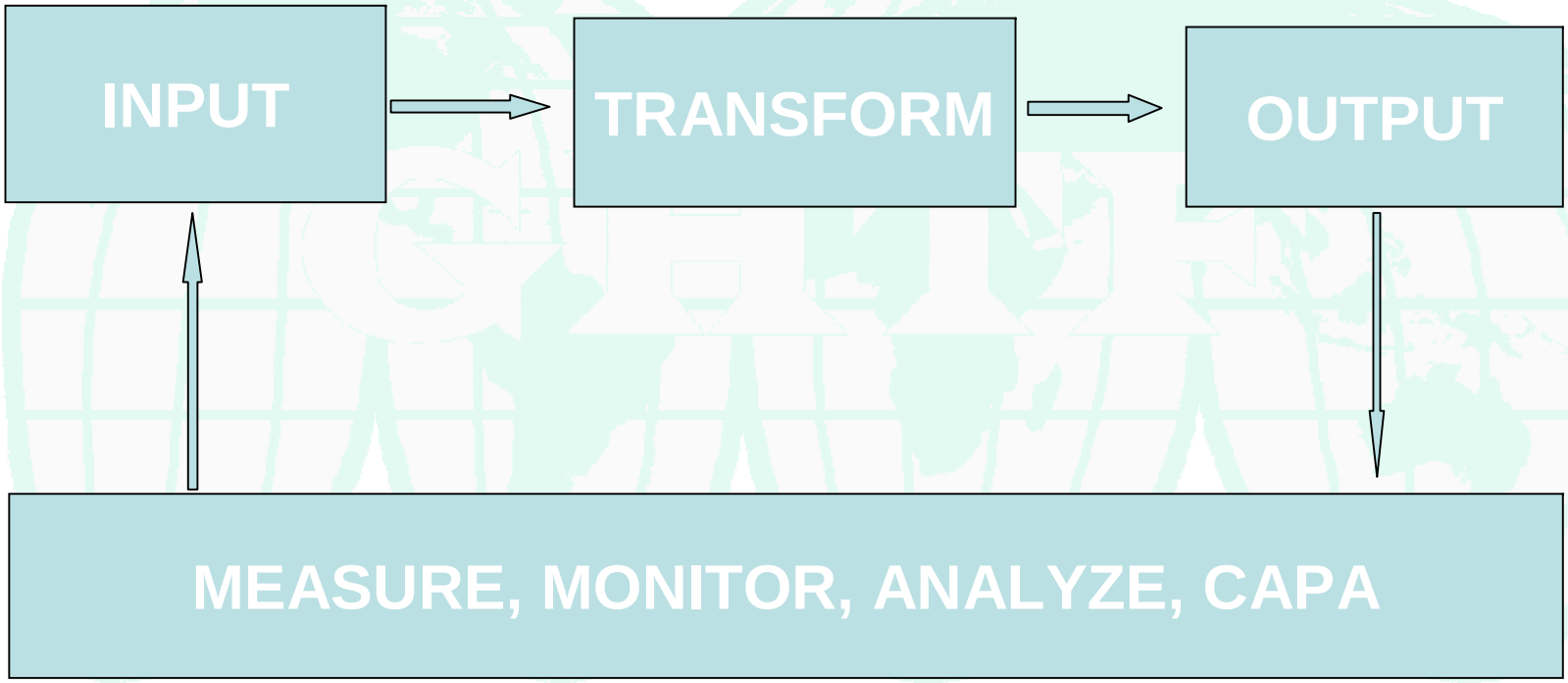
Audit Approaches

- Top-down approach
- Bottom-up approach
- Combination of these two approaches
- Horizontal Approach

Process Based Auditing

Check if all subsystems and processes of the quality management system are structured as a self-regulating control process – for example according to Deming‘s PDCA cycle: **P**lan, **D**o, **C**heck, **A**ct

Process Based Auditing



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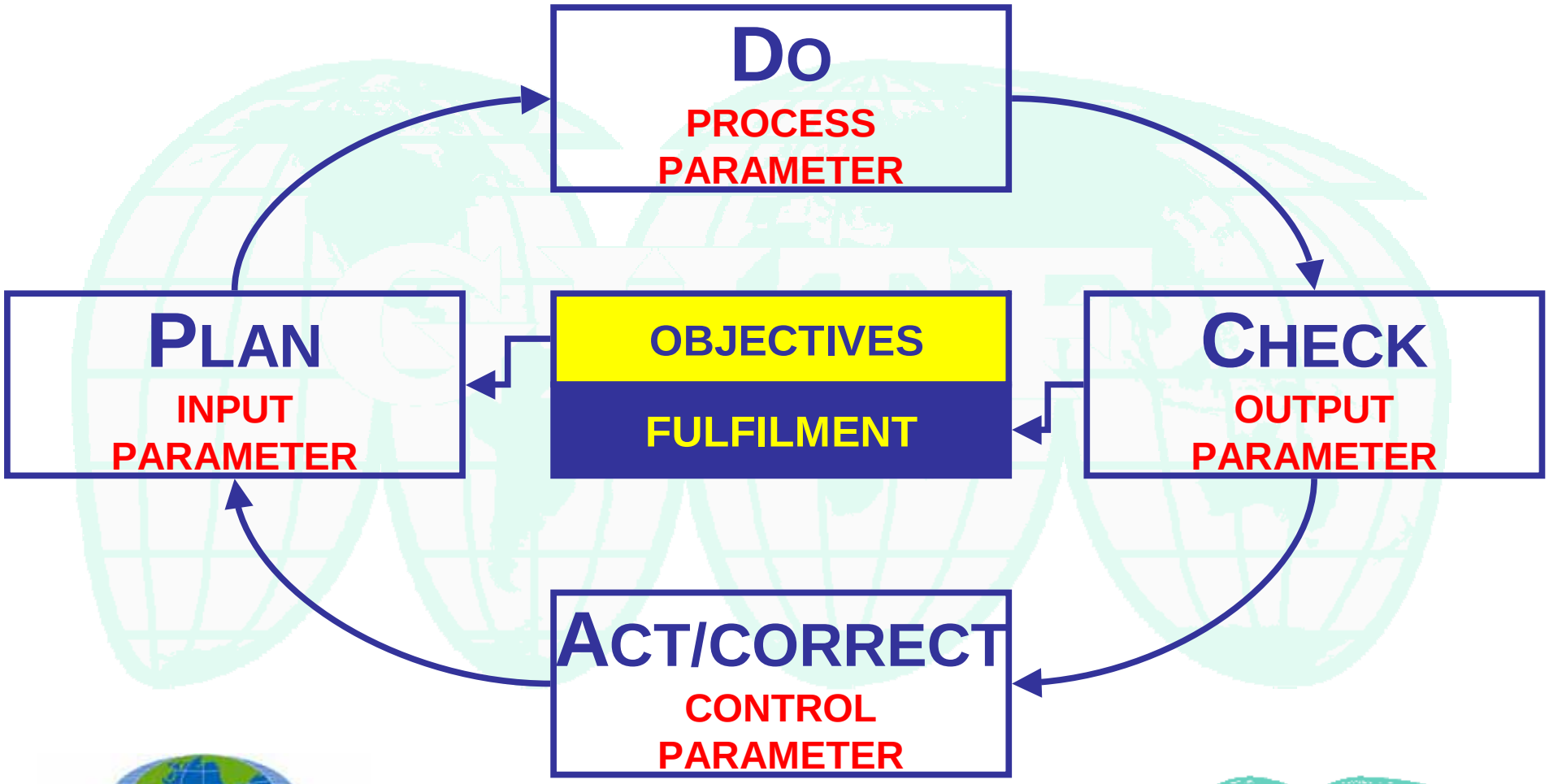
Plan, Do, Check, Act

- Has the manufacturer established the objectives and processes to enable the quality system to deliver the results in accordance with the regulatory requirements?
- Has the manufacturer implemented the quality system and the processes?
- Has the manufacturer checked process monitoring and measurement results against the objectives and the regulatory requirements? Does the manufacturer evaluate the effectiveness of the quality system periodically through internal audits and management reviews?
- Has the manufacturer implemented effective corrective and preventive actions? Confirm that the company is committed to providing high quality safe and effective medical devices, and that the company is conforming with applicable laws and regulations.

Deming - PDCA - Cycle



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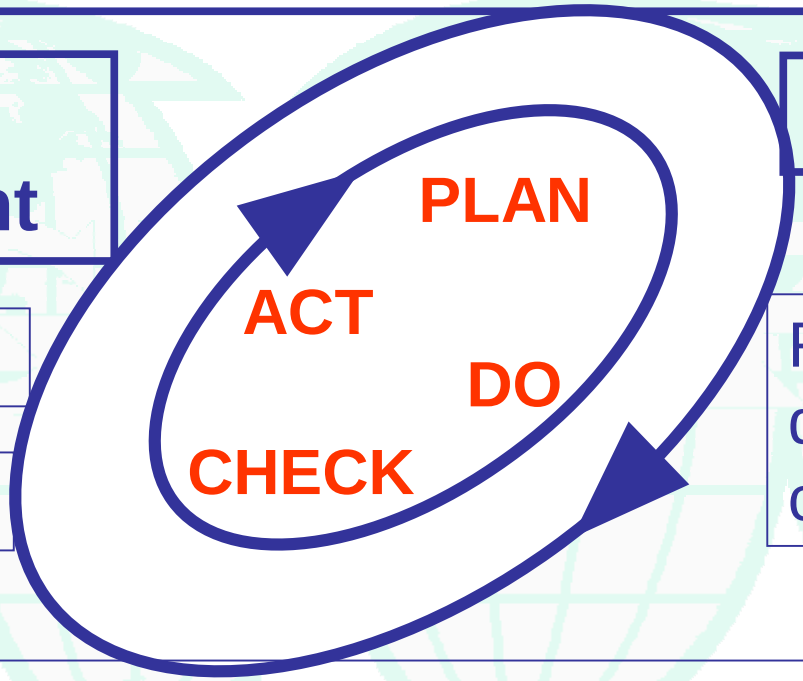
Regulatory Audit of the Quality System

Start - Management controls - Stop

Process management

Design controls

Material controls



CAPA

Records, documents, change controls

Production and process controls

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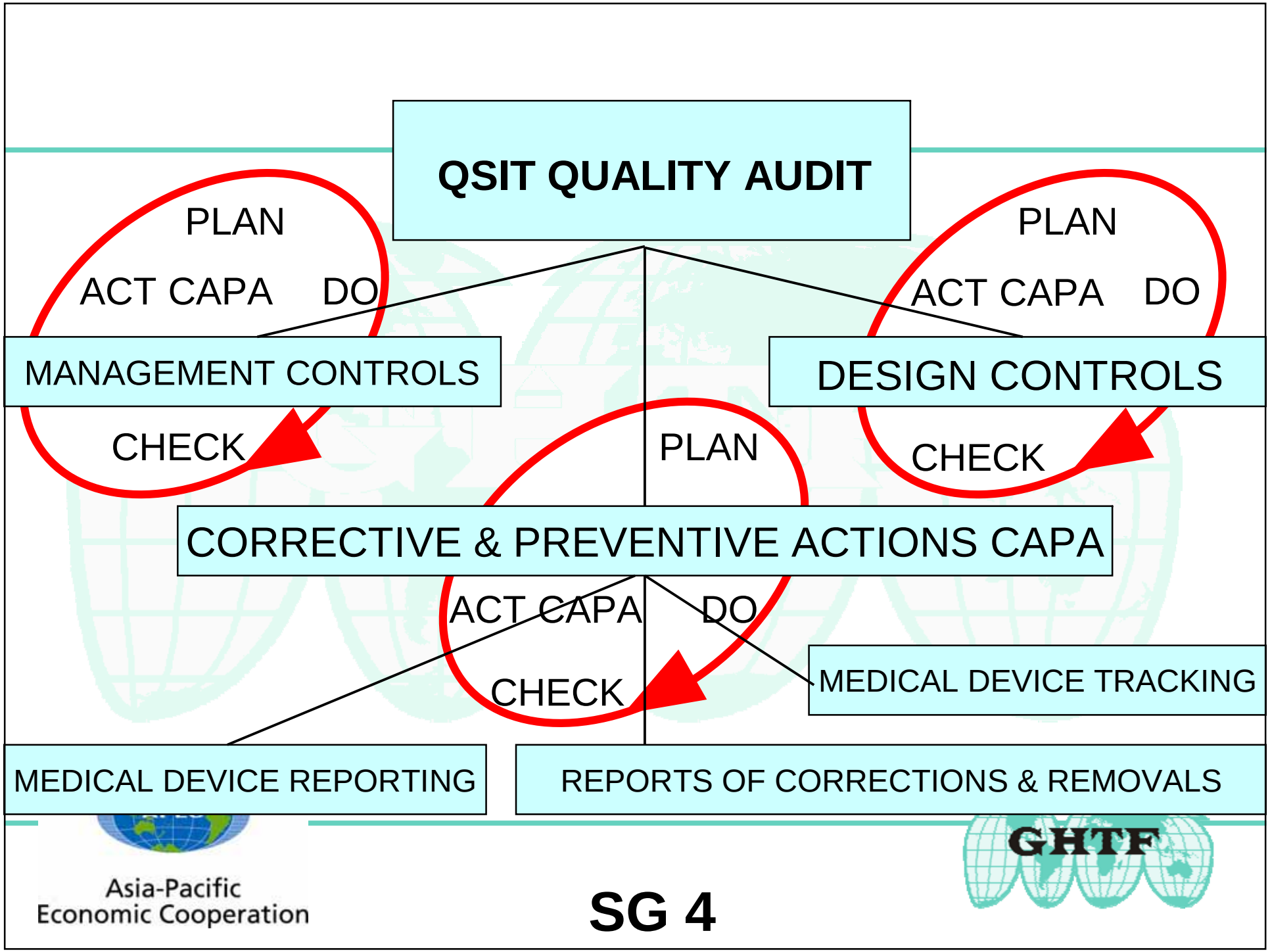

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Appendix 1 - Sampling

- Binomial Sampling Plans
- CONFIDENCE LIMIT 95% Or 99%

TABLE 1
BINOMINAL STAGED SAMPLING PLANS
BINOMAL CONFIDENCE LEVELS
*ucl = Upper Confidence Level

Confidence Limits .95<		0 out of:	1 out of:	2 out of:
A	.30 ucl*	11	17	22
B	.25 ucl	13	20	27
C	.20 ucl	17	26	34
D	.15 ucl	23	35	46
E	.10 ucl	35	52	72
F	.05 ucl	72	115	157

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TABLE 2
BINOMINAL STAGED SAMPLING PLANS
BINOMAL CONFIDENCE LEVELS
*ucl = Upper Confidence Level

Confidence Limits .99<		0 out of:	1 out of:	2 out of:
A	.30 ucl*	15	22	27
B	.25 ucl	19	27	34
C	.20 ucl	24	34	43
D	.15 ucl	35	47	59
E	.10 ucl	51	73	90
F	.05 ucl	107	161	190

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Appendix 2 -Audit Duration

- Increase
- Reduce
- Multi-Site
- Other

Appendix 3 - Sterilization

- Processes Planned, Monitored & Controlled
- Selection of Process
- Validation
- Biological Indicators
- Limits
- SW
- Equipment Status
- Personnel Training

Regulatory Auditing Strategy

- Will be revised to provide guidance for regulatory auditing of risk management activities within the quality system

SG 4 Guidance Under Development

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

(Working Draft)

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Audit Reports

- **Purpose:** To provide a format for reporting the results of an audit
- Having a common report format agreed upon by GHTF members can encourage members to share audit reports

Audit Reports

- Will provide harmonized content for reporting results of regulatory audits of quality systems
- Purpose is to facilitate the exchange of regulatory audit reports among regulatory authorities

Audit Reports – First Steps

Reporting requirements in different GHTF-regions are identified

- ⇨ Administrative data
- ⇨ Contents of the audit report

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Case Study

AUDITING

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