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FINAL DOCUMENT

Title: Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements

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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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Foreword

"Guidelines for regulatory auditing of quality systems of medical device manufacturers: part 1; general requirements" has been endorsed by the Global Harmonisation Task Force as a Final Document. It has been prepared by Study Group 4, auditing and is a consensus.

In February 1998, the GHTF Proposed Document version (SG4(98)24) was made available to other agencies through the participating regulatory bodies and trade associations in order to solicit comments. At the same time, it was also made available, in the public domain, through the UK Medical Devices Agency home page on the Internet. Study Group 4 reviewed the comments received and as a result amendments were incorporated into this document.

Comments or suggestions for changes to this Final Document should be sent to the Convenor of Study Group 4 (for address details, see below).

Global Harmonisation Task Force documents

All documents produced through the Global Harmonisation Task Force (GHTF) for medical devices represent the informal advice of participating manufacturers, other participants, and government officials as to useful practices concerning the subject matter.

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As with international standards, GHTF documents do not, by themselves, have official status but are intended to offer sound advice. The expectation is, however, that governments, through applicable procedures, may wish to give GHTF documents official status.

GHTF documents are freely available to interested parties at all stages of their development (Working Drafts, Proposed Documents and Final Documents) and are considered to be in the public domain.

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1. Introduction

This document has been prepared by Study Group 4: Auditing which was convened by the Global Harmonisation Task Force. The members of this group were auditing experts from, or acting on behalf of, regulatory bodies and representatives of the medical device manufacturing industries from Australia, Canada, Europe, Japan and the USA. A list of the organisations represented on the Study Group can be found in Annex A.

The incorporation of *quality system* requirements, based on ISO 9001/9002/9003, into regulations applicable to *manufacturers* of medical devices, provides the opportunity for developing mechanisms that would lead to global harmonisation.

In preparing this document, the group's objective was to contribute to the process of global harmonisation of regulatory *quality system* auditing of *manufacturers* of medical devices. Other regulatory bodies are invited to take advantage of the experience embodied in these guidelines when considering introducing regulatory systems for medical devices in which compliance with *quality system* requirements is to be an element of the regulations.

This document has been written for *auditing organisations*. However, it may also assist the medical device *manufacturer* to prepare for, facilitate and respond to the applicable regulatory *audits*.

The beneficiaries of the regulatory *audit* and the deliverables are as follows:

a) for the patient/user,

- a high degree of assurance that only safe and effective medical devices will be available;

b) for the regulatory body,

- a high degree of assurance (along with technical evaluation, where required in addition) of safe and effective devices;
- reliable, objective evaluation of compliance with *regulatory requirements* of the *manufacturer*'s *quality system*;

c) for the *manufacturer*,

- independent evaluation of *quality system* effectiveness and compliance with *regulatory requirements*;
- if satisfactory, results are evidence (or part thereof) of compliance with *regulatory requirement*s necessary to market devices.

Note 1. Terms written in italics in the main body of the document text are defined in section 4. Definitions.

Note 2. The auditing of a medical device manufacturer's quality system may represent only one part of the conformity assessment procedure required by the applicable regulations.

2. Scope

This document provides guidelines for *auditing organisations* responsible for establishing, planning, carrying out and documenting *audits* of *quality systems* to address *regulatory requirements* for *manufacturers* of medical devices. In addition, it describes the competence criteria that the *audit* team should meet.

The document also covers related requirements on the *audit* report and follow-up on corrective actions.

Non-regulatory quality management issues, as may be part of total quality management activities, are excluded.

3. Reference documents

This document is based on the principles in all three parts of ISO 10011:1990 and the auditing principles in ISO 14000 series (see Annex E).

Note 3. References to relevant regulations applicable to manufacturers of medical devices which include compliance with quality system requirements are listed in Annex B.

4. Definitions

Reference should be made to the definitions given in:

- the relevant *regulatory requirements*,
- ISO 8402:1994 and ISO 10011-1:1990, together with those below.

All the definitions below are for the purpose of these guidelines.

Note 4. Some terms in ISO 8402:1994 are repeated here and the source is indicated in square brackets [ ].

4.1 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].

For the purpose of these guidelines, "audit" means *audit* of the *auditee's* (see 4.2) *quality system* to determine compliance with the relevant *regulatory requirement*s.

Note 5. When addressing the regulatory requirements the term 'inspection' has been used to indicate the same meaning as the term 'audit'.

4.2 Auditee

Any organisation whose quality systems are to be audited for compliance with the relevant medical device *regulatory requirements*.

Note 6. This can be the manufacturer and/or their subcontractor(s).

4.3 Auditing organisation

A body designated, on the basis of specific regulations, to carry out *audit*s according to assigned tasks.

Note 7. Relevant auditing organisations responsible for enforcement of the regulations listed in Annex B are given in Annex C.

4.4 Auditor

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

4.5 Lead auditor

An *auditor* designated to manage an *audit* (also known as an *audit* team leader).

4.6 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'.

Note 9. Definitions of 'manufacturer' applicable to the regulations listed in Annex B are given in Annex D.

Note 10: In some internationally recognised Standards and Guidelines on auditing, specific responsibilities are assigned to the client (i.e. a person or the organisation requesting or commissioning the audit). These responsibilities are assigned on the basis that the client, as the financial supporter and primary customer of the audit, has the ultimate authority regarding the audit.

The ultimate authority for the audit of medical device manufacturers is the auditing organisation and the term “client” is not used therefore in these guidelines. .

4.7 Nonconformity

The non fulfilment of specified requirements within the planned arrangements.

Other terms may be used to mean the same as nonconformity (e.g. 'non-compliance', 'deficiency').

4.8 Objective evidence

Verifiable information or records pertaining to the quality of an item or service or to the existence and implementation of a *quality system* element, which is based on visual observation, measurement or test.

4.9 Quality audit observation

Statement of fact made during a quality *audit* and substantiated by *objective evidence*.

4.10 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.

4.11 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*.

Note 11. Guidelines, notes, draft documents, or the like should not be used as regulatory documents and are not to be construed as such unless formally promulgated.

4.12 Subcontractor

An entity, separate from the *manufacturer*, that provides to the *manufacturer* either a material, product or sub-assembly (or a component) to a proprietary specification which is incorporated into or used in the manufacture of the finished medical device or a service (e.g. testing, sterilisation) to enable the medical device to meet defined requirements. If the separate entity is owned by the *manufacturer*, it may or may not be considered a *subcontractor*, depending upon the control exercised by the *manufacturer*.

5. General principles for auditing organisations

5.1 Independence

The *auditing organisations* and their *auditors* shall be impartial and free from engagements and influences which could affect their objectivity, and in particular shall not be:

a) involved in the design, construction, marketing, installation, servicing or supply of the device categories within the scope of the *audit*;

b) involved in the design, construction, implementation or maintenance of the *quality system* being audited;

c) an authorised representative of the *manufacturer*.

Examples where independence could be compromised would include the following:

i) the *auditor* having a financial interest in the company being audited (e.g. holding stock in the company);

ii) the *auditor* being employed currently by a *manufacturer* producing medical devices.

iii) the *auditor* being a member of staff from a research or medical institute or a consultant having a commercial contract or equivalent interest with the *manufacturer* or the *manufacturer*s of similar devices.

All persons and organisations involved with an *audit* should respect and support the independence and integrity of the *auditors*.

The impartiality of the *auditing organisation* and *auditors* shall be established and documented.

5.2 Audit objectives and scope

Audit objectives and scope should be clearly defined and documented by the *auditing organisation* and the *audit* team and, as permitted by the regulatory requirements, agreed to by the *manufacturer* in the initial planning stages of the *audit*. However, based on the *quality audit observations*, the *audit* scope and objectives may be modified.

5.3 Roles, responsibilities and authorities

All the organisations involved in the *audit* process should be identified and their respective roles, responsibilities and authorities should be clearly defined and documented to:

a) ensure a clear understanding of mutual expectations throughout the *audit* process;

b) provide a means of accountability with respect to relevant *regulatory requirements*.

5.4 Resources

Adequate resources in terms of competent staff, financial support, time to conduct effective *audits* and, where necessary, access to technical information and expertise from external sources should be committed to the conduct and implementation of *audits* and all supporting *audit* activities in order to ensure that *audit* results and conclusions are of the highest possible reliability within the limitations of the sampling aspects of auditing.

5.5 Competence of the audit team

*Audit*s of medical device *manufacturers* should only be performed by *audit* teams possessing as a whole the education, skills and experience with respect to the relevant *regulatory requirements* and to the device technologies and related processes, as well as those required for auditing.

5.6 Consistency of procedures

The conduct of *audits* should be in accordance with defined and documented methodologies and techniques designed to provide consistency of approach and depth among *audits* of the same type and scope. The management of *audit* activities should be in accordance with documented, systematic procedures designed to provide the necessary technical and administrative support for the *audits*. Such procedures should be designed to comply with the applicable *regulatory requirements* and align with these Guidelines. See also clause 11.1.2

5.7 Adequacy of audit documentation

Documentation associated with each *audit* shall be maintained in accordance with applicable *regulatory requirements* and be sufficient to:

a) provide adequate information to the appropriate regulatory authorities to be used, if necessary, in pre-market approval or post market surveillance activities; and

b) ensure traceability and continuity between the successive *audits* of the same system; and

c) provide a basis for corrective action and opportunities for quality improvement to the *manufacturer*.

5.8 Confidentiality, due professional care and code of ethics

The confidentiality of all documents and information obtained in association with an *audit* should be safeguarded. There should be no disclosure of such documents and information to a third party without the express approval of the *auditee*, unless it is a *regulatory requirement*.

Due professional care, diligence and good judgement should be practised at all times in the conduct of an *audit* and in the management of supporting activities in accordance with an established and documented code of ethics.

5.9 Audit results and conclusions

The results and conclusions of *audits* should be consistent and accurate regardless of the *auditors* or the *auditing organisation* involved, to provide the beneficiaries of the *audit* with the necessary level of confidence in the output. Such conclusions are subject to the normal limitations of an *audit* as the *objective evidence* collected during the *audit* is a sample not normally based on a statistical rationale.

5.10 Quality system

Auditing organisations should implement and maintain a *quality system* to ensure that the *audits* conducted are of the highest quality in accordance with these general principles and to facilitate continuous improvement.

6. Audit objectives

Audits are designed to:

a) determine conformance of a *manufacturer*'s *quality system* with *regulatory requirements;*

b) determine the effectiveness of the implemented *quality system* for the purposes of meeting specified quality objectives which include all of the appropriate medical device *regulatory requirements*;

c) *audit* the *quality system* as the *manufacturer* has defined it (c.f.,note 12 below);

d) in the case of *audits* subsequent to the initial *audit*, ensure that corrective actions agreed as a result of the previous *audit* have been completed effectively.

Note 12. A manufacturer may have a quality system that is more extensive than that defined in the regulations.

7. Audit scope

The *audit* scope describes the extent and the boundaries of the *audit* in terms of:

a) the subject medical devices controlled by the *quality system* to be audited;

b) the *quality system* requirements against which the *quality system* is to be audited;

c) the type of *audit* required (initial, surveillance or special);

d) physical location of activities and documentation to be audited.

Audits for regulatory purposes should not impose an increase in the scope of *quality system* requirements over and above those necessary to meet *regulatory requirements*.

8. Types of audit

8.1 Initial audit

An initial *audit*, when applicable for confirmation of conformance with *regulatory requirements*, will generally be an *audit* of all elements of the *quality system (see 6.c)*.

8.2 Surveillance audit

A surveillance *audit* for a previously audited facility can either constitute a full *audit* or partial *audit* of the *quality system*.

The time interval between surveillance *audits* will depend upon:

a) the risk associated with the intended use of the medical devices;

b) the number of the *quality system* elements to be examined;

c) the nature of the *quality system* elements to be examined;

d) the scope and results of the previous *audits*;

e) the post market surveillance data available on the subject devices indicating a possible deficiency in the *quality system*;

The time interval between surveillance *audits* should not be greater than 3 years but in the case of high risk devices not greater than 2 years.

If partial *audits* are used for surveillance, within a maximum period of 5 years all elements of the *quality system* should be audited.

Note 13. Auditing organisations may specify certain aspects of the quality system which are always included in a partial audit (e.g. corrective action or follow-up of quality audit observations from the last audit).

8.3 Special audit

These *audits* may be required when:

a) external factors apply such as:

i) available post-market surveillance data on the subject devices indicate a possible significant deficiency in the *quality system*;

ii) significant safety related information becoming known to the *auditing organisation*.

b) significant changes occur to a *manufacturer*, which have been submitted as required by the regulations or become known to the *auditing organisation*, and which could affect the decision on the *manufacturer*'s state of compliance with the *regulatory requirements*.

The following are examples of such changes which could be significant and relevant to the *auditing organisation* when considering that a special *audit* is required, although none of these changes should automatically trigger a special *audit* :

i) Modifications to the *manufacturer*'s *quality system* policies caused by:

- new ownership of the *manufacturer*;
- relocation of the *manufacturer*'s activities or controls to a new site;

ii) Modifications to the defined authority of the management representative that impact:

- *quality system* effectiveness or regulatory compliance;
- the capability and authority to assure that only safe and effective medical devices are released;

iii) Addition of a new device category to the manufacturing scope within the *quality system* (e.g. addition of sterile single use dialysis sets to an existing scope limited to haemodialysis equipment, or the addition of magnetic resonance imaging to an existing scope limited to ultrasound equipment);

iv) Modification of the site operation involved in the manufacturing activity (e.g. relocation of the manufacturing operation to a new site or centralising the design and/or development functions for several manufacturing sites);

v) Significant modifications to special processes (e.g. change in production from sterilisation through a *subcontractor* to an on-site facility or a change in the method of sterilisation).

8.4 Unannounced audits

An unannounced *audit* may be necessary if the *auditing organisation* has justifiable concerns about implementation of corrective actions or compliance with *regulatory requirements*.

9. Roles and responsibilities

9.1 Auditing organisation

The *auditing organisation* has the regulatory authority or is designated by the regulatory authority to perform *audits*, the results of which are evidence of compliance or non-compliance with the *regulatory requirements* for *quality systems*. Associated with this authority are the responsibilities for management and performance of all *audit* activities .

The responsibilities of the *auditing organisation* for *audit* management include:

a) complying with relevant *regulatory requirements* for *audit* management;

b) complying with these Guidelines;

c) training, selecting and supervising *auditors*;

d) establishing methods to ensure consistency in the interpretation of the *regulatory requirements*;

e) maintaining the means of providing prompt guidance which may be required by the *audit* team during the *audit*;

f) safeguarding the confidentiality of all documents and information obtained in association with the *audit*;

g) establishing and complying with a code of ethics;

h) informing the appropriate authority on decisions taken when required by the *regulatory requirements*.

Audits do not result in a transfer of the responsibility to achieve quality objectives from the *manufacturer* to the *auditing organisation*.

In conjunction with the *lead auditor*, the responsibilities of *the auditing organisation* for *audit* performance include:

i. complying with relevant *regulatory requirements* for auditing;

ii. agreeing on the scope of the *audit*, including the standards or other documents to be used, with the *manufacturer* as necessary to comply with and as permitted by the *regulatory requirements*;

iii. planning, organising, evaluating and reporting on the *audit*;

iv. selecting the *auditors*;

v. agreeing to the language of the *audit*;

vi. decision making with regard to applicable *regulatory requirements* resulting from *nonconformities* discovered during the *audit* and subsequent verification of corrective actions.

9.2 Auditors

The responsibilities of *auditors* include:

a) complying with the applicable *regulatory requirements* for auditing;

b) helping the *manufacturer* understand the *regulatory requirements*;

c) planning and carrying out assigned responsibilities objectively, effectively and efficiently within the *audit* scope and in accordance with a code of ethics for *auditors* established and documented by the *auditing organisation*;

d) co-operating with and supporting the *lead auditor*;

e) collecting, analysing and, where appropriate, documenting *objective evidence* that is relevant and sufficient to permit the establishment of conclusions regarding compliance of the *quality system* with *regulatory requirements* and the effectiveness of its implementation in meeting quality objectives;

f) establishing the extent to which the procedures, documents and other information describing or supporting the required elements of the *quality system* are known, available, understood and used by the *auditee*'s personnel;

g) remaining alert to any indications or evidence that can influence the *audit* results and possibly require more extensive auditing;

h) informing the *lead auditor* of *quality audit observations* in a timely manner;

i) assisting the *lead auditor* in preparing the report of the *audit*;

j) informing the *lead auditor* of any major obstacles encountered in performing the *audit*;

k) safeguarding the confidentiality of all documents and information obtained in association with the *audit*:

   i) when submitting such documents to the *auditing organisation* through the *lead auditor*;

   ii) treating privileged information with discretion;

l) verifying that corrective actions have been taken and have been effective:

   i) as a result of a previous *audit*;

   ii) during the *audit*, as feasible;

   iii) based on experience gained with devices on the market (e.g. post market surveillance);

   iv) based on incidents of a serious nature;

m) minimising disruption to the *auditee'*s personnel and processes during the *audit* while attaining the *audit*'s objectives.

n) complying with any health and safety or other applicable requirements of the manufacturer (see 9.3(a)).

9.2.1 Lead auditor

The *lead auditor* is ultimately responsible to the *auditing organisation* for all phases of the *audit*. The *lead auditor* shall have authority to make final decisions regarding the conduct of the *audit* and any *quality audit observations*.

The responsibilities of the *lead auditor* include, in addition to those of the *auditors*:

a) identifying the requirements of each *audit* assigned to the *lead auditor* by the *auditing organisation*;

b) assisting the *auditing organisation* with the selection of the other *audit* team members;

c) previewing the *manufacturer's quality system* description (where appropriate) for adequacy in meeting applicable *regulatory requirements*, prior to the on-site *audit*;

d) preparing the *audit* plan and working documents and briefing the *audit* team;

e) representing the *audit* team with the *auditee*'s management;

f) communicating any *nonconformities* to the *manufacturer* as soon as possible after they are identified and indicating whether such *nonconformities* may affect compliance with the *regulatory requirements*;

g) reporting to the *manufacturer* and to the *auditing organisation* any major obstacles encountered in performing the *audit* as planned;

h) preparing and presenting the *audit* results clearly and conclusively to the *manufacturer* at the closing meeting;

i) preparing and submitting the *audit* report to the *auditing organisation* in a timely manner.

9.3 Manufacturer

The responsibilities of the *manufacturer* include:

a) defining the scope of the *audit* as permitted by the *regulatory requirements*;

b) determining the method of compliance with the *regulatory requirements*;

c) informing relevant employees about the objectives and scope of the *audit*;

d) appointing responsible members of staff to accompany members of the *audit* team and ensuring that *audit* team members are aware of health, safety and other applicable requirements;

e) providing all resources needed for the *audit* team in order to ensure an effective and efficient *audit* process;

f) providing access to the facilities and evidential material pursuant to the *regulatory requirements* as requested by the *auditors*;

g) co-operating with the *auditors* to permit the *audit* objectives to be achieved;

h) receiving the *quality audit observations*;

i) determining what follow-up corrective actions are to be taken to address *nonconformities* and other *quality audit observations* identified during the *audit*, implementing such actions in a timely and effective manner and informing the *audit organisation* as required;

j) informing the *auditing organisation* of any significant change to the *quality system* as required by the *regulatory requirements*;

k) informing any other *auditees* that may be affected by the *audit*, of its objectives, scope and any other relevant arrangements (see also clause 9.4).

9.4 Auditees

Where *auditees*, other than the *manufacturer*, are involved in the *audit* (i.e. *subcontractors*), clause 9.3, sections (c) to (g) apply. In such cases, the responsibilities for the other items remain with the *manufacturer*.

10. Audit team

10.1 Audit team composition

The *audit* team shall include a *lead auditor* who shall be in overall charge of the *audit* team. Where the *audit* team is comprised of one individual then this person shall be the *lead auditor*. The *lead auditor* should have the capability and experience to manage an *audit*.

The *audit* team shall include one or more persons with experience of assessing the relevant medical device technology incorporated in the manufactured products and the associated manufacturing processes. Decisions with regard to the extent of inclusion of such expertise in the *audit* team should be made case by case (see also clause 10.2.1).

As permitted by the regulatory system the *audit* team may be accompanied by:

a) *audit* trainees or other personnel from the *auditing organisation*;

b) *audit* trainees or other personnel from the regulatory bodies involved;

c) observers acceptable to the *manufacturer*, *auditing organisation* and *auditors*.

These accompanying persons are not considered to be *auditors* but are bound by the same obligations of confidentiality.

As permitted by the regulatory system, when the *auditing organisation* chooses the *audit* team it may take into account the *manufacturer's* opinion on the suitability of the *auditor*(s), in particular when a conflict of interest may exist (see 5.1).

10.2 Audit team competence

10.2.1 Audit team competence criteria

The competence requirements for all *auditors* in the team should be based on the qualification criteria for *quality system auditors* (ISO 10011-2:1991, Qualification criteria for quality system auditors) as well as personal attributes (e.g. tact, diplomacy, effective communication skills).

The competence of the team as a whole should be appropriate to cover the scope of the *audit*. In particular:

a) The team should have competence (i.e. training and knowledge/experience) in the following:

   i) assessment of the *quality system* for medical device *manufacturer*s and determination of the effectiveness of its implementation;

   ii) understanding the regulations and applicable standards specific to *quality system* requirements for medical device *manufacturers*;

   iii) intended use of and risks associated with the devices being produced;

   iv) the assessment of the design, manufacturing processes and the technologies involved.

b) The competence must be present within the *audit* team as a whole but not necessarily by each member of it. In assessing the *quality systems* of *manufacturer*s the *audit* team may include additional experts in processes and technology relevant to the scope of the *audit* and ideally these experts should meet the requirements of clause 10.2.1 (a). The experts authorised by the *auditing organisation* and who are not qualified as *auditors* should only assess the processes related to their specialised knowledge and under the supervision of an *auditor*.

   Alternatively, the members of the *audit* team may be given additional training and/or specialised knowledge related to those processes and technology (e.g. the achievement of a controlled environment and validation of the sterilisation process).

c) The *lead auditor* shall be competent to plan and direct the team members so that in carrying out their separate tasks, the appropriate competence is applied effectively and fairly.

10.2.2 Audit team competence records

The *auditing organisation* shall maintain records to demonstrate the competence of its *auditors*.

10.2.3 Auditor qualifications, training and experience

In addition to basic auditing skills (clause 10.2.1), the competencies specifically required for auditing medical device *manufacturer*s may be achieved through a variety of means including a combination of qualification and one or more of the training or experience elements listed below.

a) Qualification

Auditor qualification is most likely to be in one or more of the following:

i) biology or microbiology;

ii) chemistry or biochemistry;

iii) computer and software technology;

iv) electrical, mechanical or bioengineering;

v) human physiology;

vi) medicine;

vii) pharmacy;

viii) physics or biophysics.

b) Training

Special programmes may be established for training technically qualified staff in the following:

i) understanding the *regulatory requirements* and related laws/ordinances/statutes etc.;

ii) auditing of medical device *manufacturers*' *quality systems;*

iii) understanding the design and manufacturing processes and the technologies involved;

iv) safety aspects relating to the intended use of medical devices.

c) Experience

Auditor experience is most likely to be in the following:

i) working in closely related industries and the workplace such as research and development, manufacturing;

ii) working in the application of the device technology and its use in health care services and with patients;

iii) testing the devices concerned for compliance with the relevant national or international standards;

iv) conducting performance testing, evaluation studies or clinical trials of the devices.

These competencies are to be regarded as the tools to address the relevant safety and performance aspects of the *quality system* being audited arising from the way in which the devices:

- are made, and
- how they work, and
- how they are used.

11. Audit process

The *audit* process applies to initial, surveillance and special *audits*.

11.1 Preparation

11.1.1 Notification

Where permitted by the *regulatory requirements*, the *manufacturer* should be notified in advance that an *audit* is to be conducted.

11.1.2 Preview of quality system description

As a basis for planning the *audit*, the *lead auditor* may carry out a preliminary review of the *manufacturer*'s documented methods, such as the quality manual, for meeting the *regulatory requirements*.

This preview should be considered to be part of the execution of the *audit*.

If this review reveals that the system described by the *manufacturer* is not adequate to meet the *regulatory requirements*, further resources should not be expended on the *audit* until such concerns are resolved to the satisfaction of the *auditing organisation*.

11.1.3 Site visit audit plan

There shall be a site visit *audit* plan. If permitted by the *regulatory requirements*, it should be communicated to and agreed with the *manufacturer*, preferably in advance of the site visit.

The *audit* plan should be designed to be flexible in order to permit changes in emphasis based on information gathered during the *audit*, and to permit effective use of resources.

The *audit* plan shall be prepared within the *audit* scope and objectives based on:

a) the type of *audit* to be conducted;

b) information from preview of the *quality system* description, if available;

and in the case of surveillance or special *audits*:

c) information from previous *quality system audits*;

d) available post market surveillance information.

The *audit* plan should include:

i. the *audit* scope and purpose;

ii. identification of the *manufacturer*'s management team having significant direct responsibilities regarding the *audit* scope and purpose, if available;

iii. identification of reference documents (such as the applicable *quality system* standard and, if available, the *manufacturer*'s quality manual);

iv. identification of *audit* team members;

v. the language of the *audit*;

vi. the date and place where the site visit is to be conducted;

vii. the date and place where any additional documentation is to be reviewed;

viii. identification, where possible, of the *manufacturer*'s organisational units and, where appropriate, other *auditees* to be audited;

ix. the expected time and duration for each major *audit* activity;

x. the schedule of meetings, including any necessary daily briefings, to be held with the *manufacturer*'s management;

xi. the *audit* report distribution and the expected date of issue.

Where the *manufacturer* has multiple premises covered by the *quality system,* the *audit* plan should adequately address this issue.

The *manufacturer* should establish and maintain documented procedures to ensure that purchased product or services from their *subcontractor* meet the relevant *regulatory requirements*. In duly substantiated cases when the *manufacturer* is not able to give satisfactory evidence to the *audit* team that purchased product or services meet the specified requirements, the *auditing organisation* may need, where possible, to *audit* the control of processes on the premises of the *manufacturer*'s *subcontractors* (e.g. sterilisation *subcontractors*).

11.1.3.1 Audit plan changes

During the *audit* the *lead auditor* may make changes to the *auditor*'s work assignments and to the *audit* plan in order to ensure the optimal achievement of the *audit* objectives. However, the *manufacturer* should be aware that, based on the *quality audit observations*, the plan may be modified to allow flexibility in the depth of each area investigated. The *manufacturer* should be advised of the changes.

If the *audit* objectives appear to become unattainable, the *lead auditor* should report the fact and the reasons to the *manufacturer* and the *auditing organisation*.

11.1.4 Audit team assignments

Each *audit* team member should be assigned specific tasks, such as auditing specific *quality system* elements. These assignments should be made by the *lead auditor* in consultation with the *audit* team members and should be appropriate to each *auditor*'s particular technical expertise.

11.1.5 Working documents

Working documents should be prepared by the *lead auditor* with the assistance of the other *audit* team members as appropriate. These documents should be designed in relation to the *audit* plan and are for the purpose of facilitating the collection of *objective evidence* and the reporting of *audit* results.

Working documents may include:

a) check-lists used for evaluating *quality system* compliance with applicable *regulatory requirements*;

b) forms for reporting *quality audit observations*;

c) forms for documenting supporting evidence for conclusions reached by the *auditors*.

Sample working documents should be made available to the *manufacturer* on request.

Working documents should be designed so that they do not restrict additional *audit* activities or investigations which may become necessary as a result of information gathered during the *audit*.

11.2 Audit execution

11.2.1 Opening meeting

The purpose of an opening meeting is to:

a) introduce the members of the *audit* team to the *manufacturer*'s management;

b) review the scope and the objectives of the *audit*;

c) provide a short summary of the methods and procedures to be used to conduct the *audit*;

d) establish the official communication links between the *audit* team and the *manufacturer*;

e) confirm that the resources and facilities needed by the *audit* team are available;

f) confirm the time and date for the closing meeting and any interim meetings of the *audit* team and the *manufacturer*'s management;

g) clarify any unclear details of the *audit* plan.

11.2.2 Examination

An on-site examination shall be performed by the *audit* team to:

a) determine compliance of the *manufacturer*'s documented *quality system* with the *regulatory requirements* (further to the preview as described in clause 11.1.1 as appropriate);

b) confirm implementation of the *manufacturer*'s procedures;

c) verify effectiveness of the *manufacturer's quality system*.

11.2.2.1 Depth of audit

The *audit* team should review the elements of the *quality system* as contained in the *audit* scope with respect to the *regulatory requirements*, and sample documents and records at all levels in the *quality system*. The samples chosen should reflect the risks associated with the intended use for the device, the complexity of the manufacturing technologies, the range of devices produced and any available post market surveillance data.

The *audit team* should investigate all *quality audit observations* to establish their extent, particularly if there are concerns about product safety.

11.2.2.2 Collecting objective evidence

Objective evidence should be collected through interviews, examination of documents and visual observation of activities and conditions in the areas of concern and should be verified. Information gathered through interviews may be tested by acquiring additional information from other independent sources, such as visual observation, measurements and records. Based on this *objective evidence*, *quality audit observations* should be noted where there are indications of *nonconformities*.

Objective evidence may be further documented by collecting copies of documents or, on occasion, taking photographs. Collection of evidence in this manner should be accurately recorded and acknowledged by the *auditor* and the *auditee*.

The *audit* includes collecting evidence of procedures and their implementation to determine compliance with *regulatory requirements* for post production surveillance (such as complaint handling) and, where appropriate, the design process including risk analysis and clinical evaluation.

Documents or copies collected by the *auditors* during the *audit* should be noted and acknowledged.

11.2.3 Quality audit observations

All *quality audit observations* should be recorded. *Nonconformities,* and *quality audit observations* which may become *nonconformities*, should be reviewed with the *manufacturer* as soon as possible after they are noted.

Documentation of *nonconformities* should:

a) be expressed in a clear, concise manner;

b) be supported by *objective evidence;*

c) identify the specific requirements which have not been met.

11.2.4 Non-compliance with the regulatory requirements

One or more major *nonconformities* will indicate that the *manufacturer* is not in compliance with the *regulatory requirements*. Examples of *quality audit observations* that may be classified as such *nonconformities* are as follows:

a) failure to address an applicable element of the *regulatory requirements* for *quality systems* (e.g. failure to have a complaint handling or training system);

b) failure to implement an applicable element of the *regulatory requirements* for *quality systems*;

c) an excessive number of minor *nonconformities* against an element of the *regulatory requirements* for *quality systems*;

d) failure to implement appropriate corrective and preventative action when an investigation of post market data indicates a pattern of product defects;

e) products which are put onto the market which cause undue risk to patient and/or users when the device is used according to the *manufacturer's* instructions;

f) the existence of products which clearly do not comply with the *manufacturer*'s specifications and/or the *regulatory requirements* due to defective elements in the *quality system;*

g) repeated *nonconformities* from previous *audits*.

11.2.5 Closing meeting

At the end of the *audit*, the *audit* team should hold a meeting with the *manufacturer*'s management and those responsible for the functions concerned. The main purpose of this meeting is to present *quality audit observations* to the management in such a manner as to ensure that the results of the *audit* are understood.

The *lead auditor* should present the *quality audit observations* and identify which ones are, in the opinion of the *audit* team, *nonconformities* with an explanation including an indication of their relative severity with respect to the *regulatory requirements*.

The *lead auditor* should present the *audit* team's conclusions regarding the effectiveness of the *quality system* in meeting quality objectives.

A written list of *quality audit observations*, which in the opinion of the *audit* team are *nonconformities*, should be presented to the *manufacturer*'s management.

The receipt of the above list of *nonconformities* should be acknowledged by the *manufacturer*'s management.

A date should be agreed for submission to the *audit organisation* of corrective action plans necessary to address identified *nonconformities*.

11.3 Audit report

11.3.1 Report preparation

The *audit* report should be written to provide the *auditing organisation* with a permanent record of the *audit* conducted and the *manufacturer* with information on which to base corrective action and improve its *quality system*. It should be prepared under the direction of the *lead auditor*, who is responsible for its accuracy and completeness.

11.3.2 Report content

The *audit* report should accurately reflect the content of the *audit*. It should be dated and signed by the *lead auditor*. It should either reference previously issued information or as applicable the following items:

a) the scope and objectives of the *audit*, including the processes and product groups involved;

b) details of the *audit* plan, the identification of *audit* team members and *manufacturer*'s representative(s), *audit* dates, and identification of the specific organisation audited;

c) identification of the *audit* criteria against which the *audit* was conducted (*regulatory requirements* for *quality systems*, *manufacturer's* quality manual. etc.);

d) identification of *nonconformities*, including:

   i) details of each *nonconformity*;

   ii) the *audit* criterion or the specific *regulatory requirement* to which it applies;

   iii) the relative severity with respect to *regulatory requirements*; and

   iv) the date for submission of any necessary corrective action plans.

e) the effectiveness of the *manufacturer*'s *quality system* in meeting quality objectives;

f) details of any corrective action(s) taken during the *audit*;

g) recommendation to the *auditing organisation* for follow up action including time schedule.

Confirmation of the *nonconformities* and recommendations given by the *audit* team as referred to under d), e) and g) should be provided to the *manufacturer* by the *auditing organisation* as soon as possible but not longer than 6 weeks after conclusion of the *audit*. Exceptionally, the time scale may be extended when a *quality audit observation* is to be investigated after the *audit* to verify whether or not it is a *nonconformity* and to determine its significance with respect to the *regulatory requirements*. In this case the *manufacturer* should be informed as soon as possible of the cause for the delay and a revised issue date.

11.3.3 Report distribution

The *audit* report should be transmitted or made available to the *manufacturer* by the *auditing organisation*.

The *audit* report should be issued as soon as possible within a defined time period. If it cannot be issued within the defined time period, the reasons for the delay should be given to the *manufacturer* and a revised issue date should be established when permitted by the regulatory policies of the *auditing organisation*.

11.4 Retention of audit records

The *auditing organisation* shall retain auditing documents for a period of time prescribed by the applicable *regulatory requirements*.

11.5 Audit completion

The *audit* is completed upon submission of the *audit* report to the *manufacturer*.

12. Corrective action follow-up

Corrective action and related subsequent *audits* should be completed within a time period agreed between the *manufacturer* and the *auditing organisation.* The *auditing organisation* may request from the *manufacturer* follow up reports on the implementation and results of corrective action. Such reports should be reviewed by the *auditing organisation* and the review results communicated to the *manufacturer*.

Annex A

List of organisations represented on Study Group 4: Auditing.

Australia	**Therapeutic Goods Administration**
Canada	**Health Canada**
Europe	**European Commission DG III**
	Medical Devices Agency
	Notified Bodies
	(BSi, TÜV Product Service)
	Technical Research Centre of Finland (VTT) (to January 1995)
	Norwegian Board of Health (from June 1995)
	European Industrial Federations:
	(COCIR, EUCOMED, EUROM VI etc.)
Japan	**Ministry of Health and Welfare (MHW)**
	Japan Federation of Medical Devices Associations (JFMDA)
USA	**Food and Drug Administration**
	Health Industry Manufacturers Association

Annex B

List of references to the relevant regulations applicable to manufacturers of medical devices and which include compliance with quality system requirements.

Australia

Therapeutic Goods Act, 1989. This covers both product registration and manufacturing compliance.

Therapeutic Goods (Manufacturing Principles) as currently determined.

Canada

Food and Drugs Act, R.S. c F-27, s.1

Medical Devices Regulations, Schedule 1101, effective July 1st, 1998

Paragraphs 32(2)(*f*), (3)(*f*) and (4)(*p*) of the Medical Devices Regulations, concerning quality system requirements, come into force on July 1st, 2001.

Europe

COUNCIL DIRECTIVE 90/385/EEC of 20 June 1990 concerning active implantable medical devices.

COUNCIL DIRECTIVE 93/42/EEC of 14 JUNE 1993 concerning medical devices.

Japan

Quality Assurance Standard for Medical Devices

(28 December 1994: Yakuhatsu No. 1128)

Pharmaceutical Affairs Law

USA

Title 21 Code of Federal Regulations, Part 820.

Federal Food, Drug, and Cosmetic Act, Section 520 f(1) and Section 501 (h)

Annex C

Relevant auditing organisations responsible for enforcement of the regulations listed in Annex B

Australia

Therapeutic Goods Administration

Canada

The Therapeutic Products Programme of Health Canada has the final authority for enforcement of the Act and Regulations listed in Annex B. Compliance strategy for quality systems requirements, including regulatory audit strategy, is presently under development.

Europe

Regulatory audits are conducted by Notified Bodies designated by the Member States' Competent Authorities under the Directives 90/385/EEC and 93/42/EEC. The Notified Bodies are listed in the Official Journal which is updated from time to time (e.g. OJC 172 of 15 June 1996)

Japan

The MHW takes the final responsibility for enforcement of the relevant law and regulations, and the prefectural governments implement the site audits of the medical device manufacturers.

USA

U.S. Food & Drug Administration

Annex D

Definitions of 'manufacturer' applicable to the regulations listed in Annex B.

Australia

"Manufacture", in relation to therapeutic goods, means:

(a) to produce the goods; or

(b) to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

"Manufacturing premises" means premises (including premises that comprise 2 or more sites):

(a) that are for use in the manufacture of a particular kind of therapeutic goods; and

(b) at which the same persons have control of the management of the production of the goods and the procedures for quality control.

Canada

'Manufacturer' of a medical device means a person who sells the medical device under their own name, or under a trade-mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the device, or assigning to it a purpose, whether those tasks are performed by that person or on their behalf.

Europe

Article 1: Definitions, scope: section (f)

`Manufacturer' means the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.

The obligations of this Directive to be met by manufacturers also apply to the natural or legal person who assembles, packages, processes, fully refurbishes and/or labels one or more ready-made products and/or assigns to them their intended purpose as a device with a view to their being placed on the market under his own name. This subparagraph does not apply to the person who, while not a manufacturer within the meaning of the first subparagraph, assembles or adapts devices already on the market to their intended purpose for an individual patient.

Japan

No definition of “manufacturer” exists but it can be interpreted as follows in accordance with the relevant definitions in the Pharmaceutical Affairs Law.

“Manufacturer” of medical devices means any person who industrially manufactures medical devices with a licence for manufacturing medical devices and any person who has not obtained the licence shall not industrially manufacture medical devices.

A license for manufacturing medical devices is issued by the prefectural governor under the final responsibility of the Minister of Health and Welfare and ensures that the manufacturer has the ability to manufacture the medical devices, whether the manufacturing facilities have sufficient structure or equipment, manufacturing and control procedures, and human resources to properly deal with the medical devices.

USA

Title 21 CFR Section 820.3 Definitions.

Subsection (o)

Manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilisation, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.

Annex E

References

[1] ISO 10011-1 : 1990, Guidelines for auditing quality systems - Part 1: Auditing

[2] ISO 10011-2 : 1991, Guidelines for auditing quality systems - Part 2: Qualification criteria for quality system auditors

[3] ISO 10011-3 : 1991, Guidelines for auditing quality systems - Part 3: Management of audit programmes

[4] ISO 8402 : 1994, Quality management and quality assurance - Vocabulary

[5] ISO 14011: 1996, Guidelines for Environmental Auditing – General principles

LIST OF SUPPLEMENTS

Number	Title	Study Group 4 Reference	Date
1	Audit language requirements	SG4(99)14	29/6/99