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FINAL DOCUMENT

Global Harmonization Task Force

Title: Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 4: Multiple Site Auditing

Authoring Group: Study Group 4 of the Global Harmonization Task Force

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

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Preface

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1.0 Introduction

This document gives guidance to regulators and auditing organizations conducting audits of quality management systems of medical device manufacturers with multiple sites. This document should be read in conjunction with the Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers -- Part 2: Regulatory Auditing Strategy (GHTF/SG4/N30).

In addition to the potential benefits addressed in the section 1.0 of Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers -- Part 2: Regulatory Auditing Strategy, other potential benefits of this document for the regulators or auditing organizations include:

- improved efficiency of an audit of a quality management system of a manufacturer with multiple sites
- reduced audit time and cost for the auditing organization
- provision of guidelines for initial audit, surveillance audit, and special audit of a quality management system of a manufacturer with multiple sites

Potential benefits for the manufacturer of medical devices include:

- improved efficiency of an audit of a quality management system of a manufacturer with multiple sites
- reduced audit time and cost for the manufacturer
- improved understanding of the audit of quality management system of the manufacturer with multiple sites

2.0 Scope

This document provides guidance to auditing organizations on planning, organizing, conducting, documenting, and reviewing audit programs for auditing a medical device manufacturer (see 6.5) with multiple sites operating under the same quality management system

This document does not apply to a manufacturer operating with multiple businesses employing separate and distinct quality management systems. Any relationships among these businesses need to be considered as suppliers. (See GHTF Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 5: Audits of manufacturer control of suppliers GHTF/SG4/N84)

However, if a manufacturer has multiple businesses with multiple sites, operating within one quality management system, then this document applies.

3.0 Purpose

The purposes of this document are:

- To harmonize and provide guidance on planning, organizing, conducting, documenting, and reviewing an audit program for auditing a manufacturer with multiple sites
- To assist auditors and manufacturers in preparing for, facilitating and responding to audits involving multiple sites
- To improve the efficiency of audits of a quality management system of a manufacturer with multiple sites

4.0 Rationale

This document aims to provide guidance for auditing organizations on the auditing of a quality management system of a medical device manufacturer with multiple sites.

This document promotes consistency in the planning and conducting of audits involving a medical device manufacturer with multiple sites.

5.0 References

GHTF/SG4/N28R4:2008: Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements

GHTF/SG4/N30R20:2006 Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy

GHTF/SG4/N33R16:2007 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports

GHTF/SG4/N84R13:2010 Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 5: Audits of manufacturer control of suppliers

GHTF/SG1/N055: 2009 Definitions of the Terms Manufacturer, Authorized Representative, Distributor and Importer

6.0 Definitions

6.1 Audit program

A set of one or more audits planned for a specific time frame and directed towards a specific purpose

Note: An audit program includes all activities necessary for planning, organizing and conducting the audits. (ISO 9000:2005 3.9.2)

6.2 Centralized function

A quality management system function that is applicable to one or more sites, but is controlled from a single site (which may not necessarily be the lead site)

6.3 Common function

A quality management system function defined by a single site that is applicable to more than one site and may be controlled by multiple sites

6.4 Lead site

A site having an identified central function, by which the quality management system applied to the sites is established and subject to continuous surveillance and internal audits. The lead site can require any site to implement corrective actions when needed. Where applicable this should be set out in the formal agreement between the lead site and the other sites.

6.5 Manufacturer

"Manufacturer" means any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person(s). [GHTF/SG1/N055]

6.6 Manufacturer with multiple sites

A manufacturer which conducts activities under the same quality management system at more than one site

6.7 Site

A place where a manufacturer conducts activities

6.8 Overall lead auditor

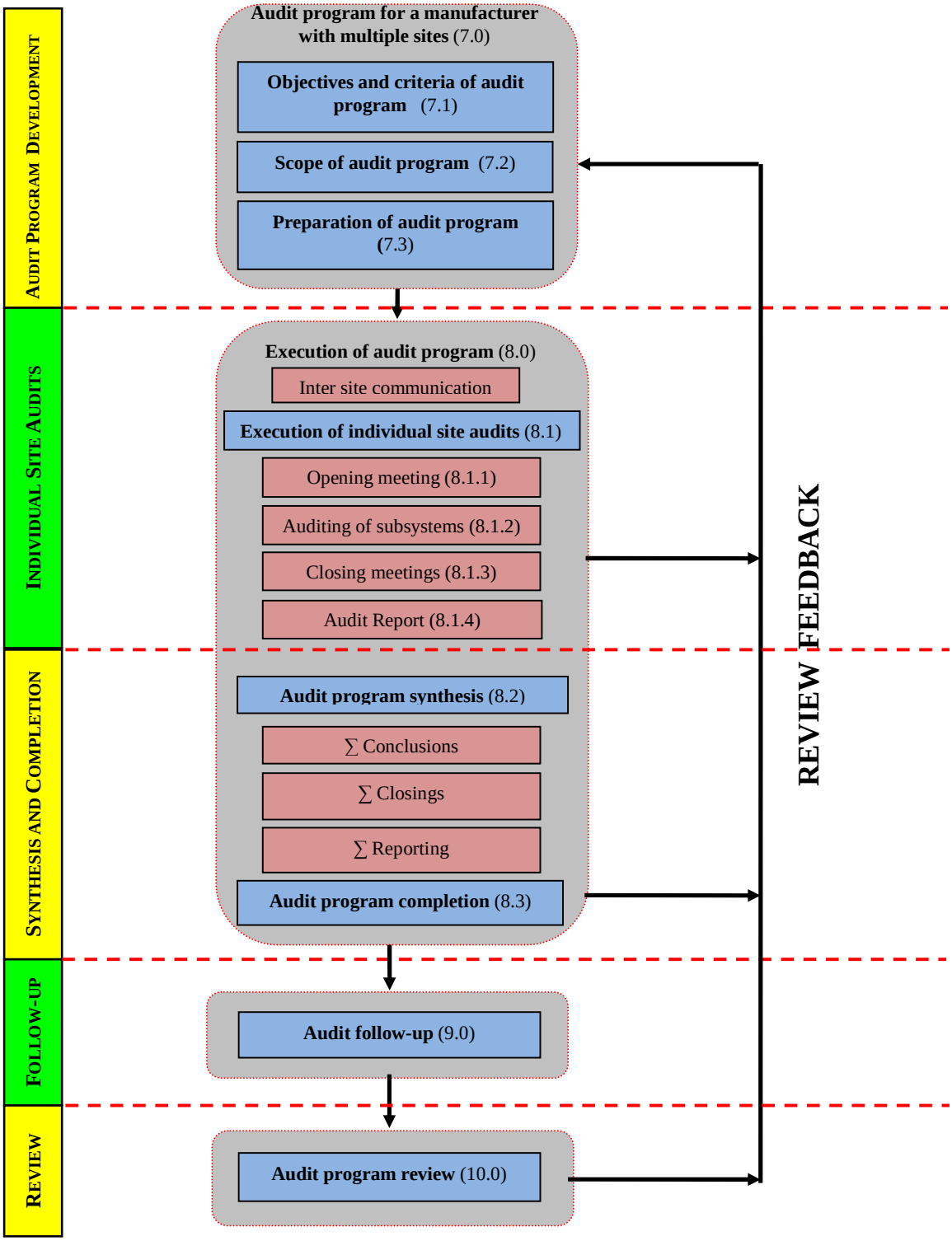
The auditor who has oversight of the audit program described in this document

7.0 Audit program for a manufacturer with multiple sites

Multiple site audits are applicable to manufacturers where activities subject to audit are carried out in the different sites and under the authority and control of a lead site. In order to effectively coordinate the audit activities of such multiple site audits a documented audit program should be developed. This should be coordinated by the overall lead auditor.

This document supplements guidance found in Section 10 of the GHTF Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers Part 1: General Requirements (GHTF/SG4/N28) and Sections 6.3, 6.6 and 7.0 of Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers Part 2: Regulatory Auditing Strategy (GHTF/SG4/N30). The relationship between these guidelines and this document is illustrated in Appendix A.

Figure 1: Process Flow for Multiple Site Auditing



7.1 Objectives and criteria of audit program

The objectives and criteria of a multiple site audit program should be established in such a way that they demonstrate appropriate coverage of a manufacturer's Quality Management System. (See GHTF/SG4/N28 10.1 and 10.6.2) The audit program should be defined considering the interfaces, links, and responsibilities among the different sites. (See GHTF/SG4/N28 10.1)

7.1.1 Audit program objectives

The audit program is designed to:

a) Determine conformity of the manufacturer's quality management system with relevant quality management standards and regulatory requirements. The legal requirements may be different in the various sites.
b) Determine the effectiveness of the implemented quality management system while avoiding redundancy of auditing the centralized functions multiple times.
c) Allow the determination of the capability and effectiveness of the manufacturer to collect and analyze data from all sites including the lead site, from sources like Management reviews, Complaints, Internal audits, Corrective actions, etc.

For more information on audit objectives, see Section 10.1.1 of GHTF/SG4/N28.

7.1.2 Audit program criteria

Audit program criteria for multiple site audits should include:

a) The regulatory requirements applicable to the lead site and to the other sites
b) The quality procedures of the manufacturer's quality management system, particularly those relating to centralized and common functions

For more information on audit criteria, see Section 10.6.2.2 of GHTF/SG4/N28.

7.2 Scope of audit program

In order to create an audit program which is appropriate for all the sites to be covered, the auditing organization should obtain sufficient information from the manufacturer and verify:

- the quality management system to be audited including the sites operating under this quality management system
- complexity and scale of the activities covered by a common quality management system
- person(s) in charge of the quality management system
- the lead site

Interactions and interfaces between sites (including the lead site), site specific activities and any variations in the local implementation should be considered including:

- management review meetings
- internal audit program
- design activities
- production activities (including storage) of a device
- CAPA system
- arrangements for post-market surveillance and data analysis
- evaluation of suppliers
- document control system
- customer feedback and analysis of the feedback

For more information on audit scope, see Section 10.1.2, 10.6.2.2 of GHTF/SG4/N28 and Section 6.6 of GHTF/SG4/N30.

7.3 Preparation of audit program

Once the overall audit program objectives and criteria have been set and the quality management system to be audited has been characterized, the audit program can be prepared and documented under the coordination of the overall lead auditor.

7.3.1 Objectives, criteria and scope of individual site audits

Section 10.1 of GHTF/SG4/N28 provides guidelines of defining audit objectives, criteria and scope. The characterization of the quality management system audited in the previous steps allows a determination of the overall scope and time frame of the audit program in terms of sites and activities to be audited. The scope of the individual site audits should therefore be based on this information. This does not preclude the combination of sites and/or activities into a single audit.

Once the scope of each of the individual site audits is set, the criteria for each audit can be delineated. The criteria are likely to be subsets of the overall audit program criteria.

Finally, audit objectives for the individual site audits are set. Objectives should include:

- verification of the implementation of the requirements
- effectiveness of the interaction and interfaces between the sites (including the lead site)
- conformity to quality management system policies across all sites

For more information on audit objectives, see Section 10.1.1 of GHTF/SG4/N28.

7.3.2 Sequence of audits

The sequence (or order) of audits to be executed as part of the audit program should be predetermined based on the need to evaluate common functions as well as interfaces. The overall auditing approach (e.g. top down, combination, product) used will strongly influence the sequence of audits.

The audit program may use several approaches to define the sequences for auditing the sites:

- **Lead site first, then other sites**
  In this approach, the audit team will audit the lead site (e.g., headquarters). After the audit of the lead site, audits of the other sites will be conducted. Depending on the results of the additional site audits, there may be a need to continue the audit at the lead site to complete the audit program.

  This approach is recommended for initial certification.

- **Other sites first, then lead site**
  In this approach, the audit team will first audit some/all of the other sites, which are a part of the overall quality management system. After the audit of some/all of these sites, the audit of the lead site will be conducted.

  This approach is recommended when the auditing team wants to focus on a specific topic or subsystem.

- **Simultaneous audits**
  In this approach, different audit teams audit multiple sites at the same time.

This approach may be used when there is a specific concern that necessitates expeditious auditing of the quality management system.

7.3.3 Determination of resource needs

The resource needs for each individual audit should be determined considering:

- role of the lead auditor in communications
- necessary auditor competencies
- auditor responsibilities
- number of audit person days required per individual site
- overall time frame for the audit program
- need for technical experts and translators
- audit program report requirements

Where practical, a single audit team should perform all site audits to ensure continuity. When this is not possible, efforts should be made to use the same lead auditor for all audit teams. During the execution of these audits, regular communication between lead auditors may be useful to ensure consistency in audit execution, as well as communication of potential issues/risks among sites.

For more information on audit team competence, see Section 9.2 of GHTF/SG4/N28.

7.3.4 Determination of communication and reporting needs

The auditing organization should ensure continuity of information between audit teams during the audit and closing meeting(s).

As part of the audit program, a communication plan should be developed and documented. The following should be considered in the communication plan:

- Information to be conveyed between individual site audit teams, auditing organization management, e.g.
    - confirming site specific activities
    - audit findings
    - audit trails
    - resources necessary for future audits based on current findings
- Communication during individual site audits and closing meeting(s);

- Limiting discussions with the manufacturer to specific findings identified at each individual site during the execution of individual site audits without presenting conclusions about the conformity of the quality management system as a whole;
- Preparation and distribution of individual and synthesis reports;
- Communication plan review and revision as necessary

Effective communication planning ensures key issues (e.g. interfaces between sites, etc.) are identified and pursued during the current and future audits.

Audit report(s) should be prepared in accordance with the guidance in GHTF/SG4/N33. As a minimum, a report for the audit program should be written to cover the assessment of the quality management system as a whole. Where site audits are close geographically, functionally or temporally, the reporting of these audits may be combined.

7.3.5 Completion of audit program preparation

A written audit program should be produced which contains all the above information, summarized as follows:

1. Audit program objectives, criteria, and scope
2. Sequence of audits to be performed
3. Objectives, scope and criteria as well as the resources needed, for each individual audit
4. Communication plan including reporting requirements

The details of the individual site audit plans can be left to the audit team leader(s) or the overall lead auditor if one is used. For more information on audit planning, see Section 6.6 of GHTF/SG4/N30.

8.0 Execution of audit program

In addition to what is defined by section 10.6 of GHTF/SG4/N28 (Audit Activities), when conducting audits of multiple sites several key factors require special consideration.

It will usually be more practical to audit centralized and common management functions first when using a top-down approach.

Centralized functions may include:

- logistic systems (inventory, warehousing, distribution)

- purchasing
- complaint handling
- quality management system documentation
- information technology systems

Conversely, using a product approach, one may first visit a design center, followed by a manufacturing facility and a distribution center.

It is recommended to keep the period between audits as short as possible, in order to ensure the information and data gathered at the different sites are current and consistent.

The audit team(s) should communicate individual site audit findings at appropriate stages during the audit program. (See section 7.3.4 above) Based on these findings the audit program should be reviewed and modified as necessary.

For a given site and a given centralized function, the auditing team should:

- evaluate the conformity and effectiveness of the activity related to this centralized function that is under responsibility of the site
- evaluate the conformity and effectiveness of the interface process with other sites

8.1 Execution of individual site audits

8.1.1 Opening meeting

In addition to what is defined by section 10.6.3.1 of GHTF/SG4/N28 for the opening meeting of a multiple site audit the following should be considered:

- Provision of a summary of the audit program for the multiple site audits
- Explanation that the site audit is one part of the multiple site audit
- Confirmation of centralized and common functions
- Identification of where functions, including centralized and common functions, are addressed

8.1.2 Auditing of subsystems

In addition to section 7.0 of GHTF/SG4/N30, the following sections serve as a guide in the audit of the various quality management subsystems.

8.1.2.1 Management subsystem

1. Determine whether there are any specific regulatory requirements that apply to the particular site (Sites in different states/countries).

2. Verify that the communication between sites is effective.

3. If the management review meetings are at the corporate level, determine how the other sites contribute to the content of the management reviews.

4. Determine who attends lead site (and other sites) management review meetings.

5. Determine whether internal audits address applicable aspects of the requirements at each site. If so, determine whether there is a common approach used by all sites.

6. Determine whether the information about the outcome of the audit is shared.

8.1.2.2 Design and development subsystem

1. Determine at which site the same procedures and methodology are followed

2. Determine how designs are transferred from the design site(s) to manufacturing site(s).

3. Verify whether development for the same product occurs at multiple sites. If so, determine how these activities are controlled and coordinated.

8.1.2.3 Product documentation subsystem

1. Verify that the arrangements between the sites for access/control of product documentation are adequate.

2. Verify that change control is adequately documented.

8.1.2.4 Production and process controls subsystem

1. If production activities (including storage) of a device occur at more than one site, determine what impact this has on product quality, consistency and preservation.

2. Verify that the responsibilities for QC are sufficiently defined to ensure that components or subsystems that are manufactured by one site meet the requirements for another site.

3. Verify that the same production activities performed at multiple sites are performed in an equivalent manner (i.e. following the same procedures, the same process validation approach, etc).

8.1.2.5 Corrective and preventive actions (CAPA) subsystem

1. Verify that relevant CAPAs and opportunities for improvement are communicated and/or implemented between sites.

2. Verify that there is adequate exchange of information about post-market surveillance and data analysis between the sites.

8.1.2.6 Purchasing controls subsystem

Determine how the sites that rely on another site to evaluate and approve suppliers on their behalf, ensure adequate supplier evaluations and control.

8.1.2.7 Documentation and records subsystem

1. Verify that centralized documentation processes and documents are implemented.

2. Determine if each site manages site specific documentation in accordance with centralized or local quality management system policies on the subject. .

3. Determine whether the document retention practices are the same for all sites (e.g. the requirements could differ according to the local regulations) and meet the audit criteria.

4. Verify that the site specific documentation does not conflict with centralized documentation.

8.1.2.8 Customer related processes subsystem

1. Determine whether customer feedback and analysis of the feedback is centralized (corporate) and/or site specific. If centralized, the system needs to be accessible to the site as well.

2. Verify that there is an adequate and timely exchange of information between the appropriate sites (e.g., to meet adverse event reporting requirements).

8.1.3 Closing meetings

Closing meeting(s) are held as defined in the original audit program plan and may be held at individual site(s) or solely at the completion of the audit program.

If individual site audit closing meetings are held, discussions should be limited to specific findings identified at each individual site without presenting conclusions about the conformity of the quality management system as a whole.

In addition to guidance contained within section 10.6.3.5 of GHTF/SG4/N28 (Closing Meeting), individual site audit closing meetings should:

- Ensure management of lead site is informed about results at site audit
- Explain whether findings are limited to the audited site
- Explain that the site audit is one part of the multiple site audit

8.1.4 Audit report

If site audit reports are being generated, the audit report for the individual site audit should be prepared in accordance with SG4 N33. The report should be limited to specific findings identified at each individual site without presenting conclusions about the conformity of the quality management system as a whole.

Although reports are usually site specific, there may be occasions where there will be one audit report covering more than one site.

8.2 Audit program synthesis

8.2.1 Communication of overall findings

In addition to section 10.6.3.5 of SG4 N28, the overall findings and conclusions for the quality management system may be presented at a meeting, or by alternate appropriate communication methods.

During this communication, the auditing organization (the overall lead auditor) and the manufacturer should discuss how the post audit activities will be communicated and managed.

If a closing meeting is held at the end of the audit program for the multiple sites, it should:

- Ensure management of lead site is informed about results at site audits
- Synthesize individual site findings
- Present conclusions about the conformity of the quality management system as a whole
- Communicate effectiveness of the interactions among the sites

8.2.2 Synthesis Report

In addition to section 8.0 of GHTF/SG4/N33, a report should be generated which includes conclusions with regard to the overall objectives listed in section 7.1 above. This report may be referred to as a synthesis report.

The report may be presented to the manufacturer at a meeting or by alternate agreed upon communication methods.

The overall lead auditor should consolidate the findings from all the individual site audits and produce a synthesis report. Evaluation of individual site audit findings initially considered as minor nonconformities should be reviewed to ensure they do not indicate a major nonconformity within the overall quality management system.

The synthesis report should reference all audited locations and summarize the overall results and conclusions. The report can reference individual site audit reports for specific findings and non-conformities that are only applicable to one site. The report should address the interfaces between sites and pay particular attention to centralized and common functions. There should be indication of the number of employees, person-days of audit, relevant processes, products, quality management standards and national requirements for the individual sites. This information may be presented in a table or matrix.

8.3 Audit program completion

The audit program is completed when all the activities in the audit program plan have
been completed and the final audit report(s) have been submitted to the manufacturer.

9.0 Audit follow-up

In addition to section 10.8 of GHTF/SG4/N28, the evaluation of the manufacturer's corrective actions will include the considerations outlined below.

When a nonconformity is found at any individual site (or with site interfaces) by the auditing organization, the manufacturer should investigate whether other sites may be affected, perhaps indicating an overall system deficiency. Similarly, the auditing organization may identify a major nonconformity in its synthesis report.

If a systemic issue does exist, the manufacturer should perform analysis, correction, and corrective action and verification at the lead site and the affected sites. The auditing organization should review the manufacturer's plans for comprehensiveness and review the completion and effectiveness of corrective actions. This verification may be part of subsequent audits and/or form inputs to the next audit program.

Where a manufacturer decides to limit its corrective action or preventive action, they should provide a compelling justification to the auditing organization.

10.0 Audit program review

Following implementation, the audit program should be systematically reviewed. The objectives of this review are:

- to assess the effectiveness of the audit program
- to modify the audit program if it is subject to further implementation
- to undertake any correction or corrective action should the audit program prove deficient in any way

10.1 Audit program effectiveness assessment

When assessing the effectiveness of the audit program, the following questions should be answered:

1. Have the overall audit program objectives been accomplished?
2. Did the audit program allow complete coverage of all the audit criteria?
3. Were the scope, objectives, and criteria of the individual site audits adequate?
4. Was the sequence of audits appropriate?
5. Was the auditing approach appropriate?

6. Did the audit program allow the audit team to examine the interface and interaction between the different sites in an appropriate fashion?
7. Were the resources allocated to the audit program sufficient?
8. Did the audit program optimize the use of resources?
9. Was audit reporting adequate?

Where assessment of the effectiveness of the audit program reveals deficiencies, it may be necessary to undertake correction and corrective action. Corrective action may include modification of future audit programs or performance of additional audits to ensure the manufacturer's compliance.

10.2 Modifying the audit program

If the audit program is to be used again, results of the assessment of the effectiveness of the audit program may be used to modify the audit program. Modifications could include a change in the sequence of audits, addition of resources, or changes in the reporting requirements. Modifications to the audit program should always be framed in the context of the overall objectives of the program.

10.3 Correction and corrective action

In cases where the assessment of the effectiveness of the audit program reveals deficiencies and the program is not to be used again, it may be necessary to undertake correction and corrective action.

Correction should consist of activities to bridge the gap between what was accomplished as part of the audit program and what the overall objectives of the program are. This may entail additional site audits or follow-up audits or the preparation of additional reports. In extreme cases, the scope of approvals resulting from the audits may need to be reduced.

Corrective action taken in respect of audit program deficiencies should focus on the process by which the audit program is elaborated. Changes in the approach used to characterize the quality management system may need to be executed. Corrective action may also affect the way resources are allocated to the audit program, or the way audit objectives and criteria for individual site audits are set.

Appendix A: Flow chart showing relationships among all SG4 guidelines