



*White Paper:*

# The Value of Studying and Utilizing FDA's QSIT Manual

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## INTRODUCTION

In 1992 the United States entered into the *Global Harmonization Initiative*, and the Global Harmonization Task Force (GHTF) was formed with representatives from Japan, the European Union, Australia, Canada, and the United States in an effort to harmonize the 1978 Good Manufacturing Practices (cGMP) regulation for the medical device industry with ANSI/ISO/ASQC Q9001-1994–*Quality Systems – Model for Quality Assurance in Design, Development, Production, Installation, and Servicing*, and the ISO draft international standard (ISO/DIS 13485). In an effort to encourage FDA to work with foreign countries toward mutual recognition of cGMP requirements and be as consistent as possible with international standards, the GHTF adopted a step-wise approach toward harmonization, with the establishment of four objectives:

**Objective #1:** The harmonization of quality system requirements with ISO 9001 as a building block of all future work in harmonizing quality system requirements recognized around the world.

Current Status of this Objective: *Publication of 21 CFR Part 820 – Quality System Regulation (QSR) – October, 1996*

**Objective #2:** Harmonization of regulatory auditing or compliance inspections.

Current Status of this Objective: *Publication of “Quality System Inspection Techniques” (QSIT) – August, 1999*

**Objective #3:** The harmonization of the policy, interpretation, and regulatory consequences of noncompliance with quality system requirements in the United States, and in counterpart requirements of other countries.

Current Status of this Objective: *The actualization of this goal is still on-going.*

**Objective #4:** The mutual recognition of inspections and utilization of qualified third parties to perform inspections.

Current Status of this Objective: *On-going negotiation of mutual recognition agreements between all parties.*

## PURPOSE OF THIS WHITE PAPER

The purpose of this white paper is to discuss the role and value of the QSIT Manual to Medical Device manufacturers in performing compliance Gap Analysis, conducting Internal Audits, and in preparation for FDA Inspections.

## WHAT IS QSIT



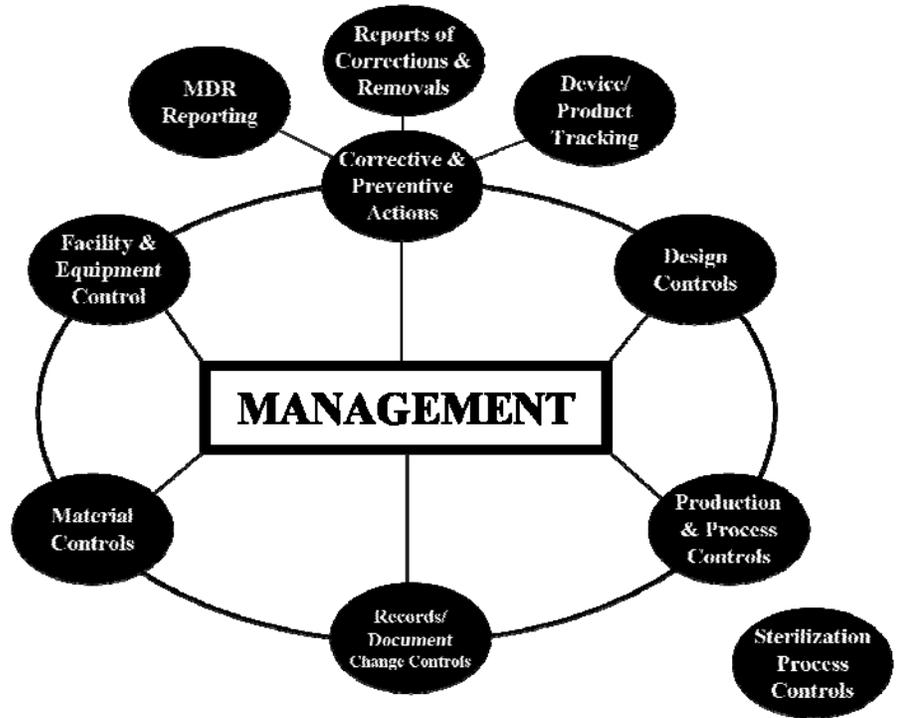
QSIT, an acronym for **Q**uality **S**ystems **I**nspection **T**echnique, is a published guide to Inspections of Quality Systems of Medical Device Manufacturers written to provide guidance to the FDA field staff on the inspectional process that may be used to assess a medical device manufacturer's compliance with the Quality System Regulation and related regulations in order to ensure the safety and efficacy of medical devices. It outlines the pre-determine Quality System oriented regimen for conducting an inspection, and subsequently becomes a reliable tool to assess preparedness and compliance.

The illustration to the right shows the seven subsystems, along with the related “satellite” programs.

1. Management Controls
2. Corrective and Preventive Action
3. Design Controls
4. Production & Process Controls
5. Records/Document Change Controls
6. Material Controls
7. Facility & Equipment Controls

Four major subsystems have been selected as the basic foundation of a firm’s Quality Management System:

1. Management Control;
2. Corrective and Preventive Actions (CAPA) [with 3 satellites: Medical Device Reporting, Reports of Corrections and Removals, and Medical Device tracking];
3. Design Controls
4. Production and Process Controls (P&PC) [with one satellite: Sterilization Process Controls].



Field investigators may conduct an efficient and effective comprehensive inspection using this QSIT Guide to Inspections of Quality Systems which will help them focus on key elements of a firm’s quality system.

The QSIT approach to FDA Inspections embraces a top-down inspection of a firm’s Quality Management System, and is therefore, a valuable tool to personnel responsible for compliance, legal, management, quality, regulatory, and technical personnel who directly interface with FDA during inspections. It is also valuable for anyone who needs to become familiar with FDA Quality System Inspection Techniques (QSIT), especially those involved with management controls, design controls, corrective and preventive actions, and production and process controls, the four QSIT focus areas.

## FDA’S NEW QSIT APPROACH TO INSPECTIONS

### “Top Down”



**Review Design Control Procedures**



**Sample Design Control Records**



**Review Design Control Records**

**Table 1**  
Binomial Staged Sampling Plans  
Binomial Confidence Levels

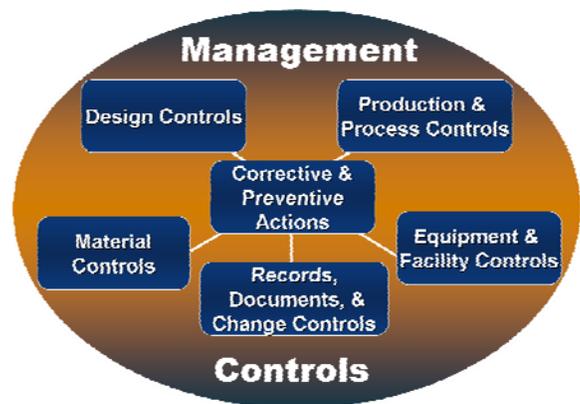
Confidence Limit	0 out of:	1 out of:	2 out of:
.95c			
A .30 ac <sup>2</sup>	11	17	??
B .25 ac <sup>1</sup>	13	20	??
C .20 ac <sup>1</sup>	17	26	34
D .15 ac <sup>1</sup>	23	35	46
E .10 ac <sup>1</sup>	35	52	72
F .05 ac <sup>1</sup>	72	115	157



Quality based on quality control activities (i.e., inspections) is costly and ineffective, as it is not possible to inspect quality into a product. It costs just as much to make a bad unit as a good one...100% inspection is costly, and most of the time, not feasible...it is often impossible to evaluate all aspects of a product. By the same token, the old FDA “Quality Control” approach to inspections was costly and ineffective. A bottom-up approach often left many stones unturned. The FDA realized the need to adopt a “Quality Assurance” approach to the process of conducting inspections...a systems approach.

The publication and implementation of the newly harmonized Quality System Regulations (QSRs), required medical device manufacturers to establish and maintain a Quality Management System (QMS) modeled after the international quality standards (i.e., ISO 9001:1994), employing a quality assurance approach of developing reliable and repeatable systems...systems of prevention rather than systems of detection. Now, to complete the circle, the FDA needed to adopt a similar approach to their inspections of Medical Device manufacturers. Becoming increasingly aware of the ineffectiveness and inefficiency of the un-systematic bottom-up, back-end “quality control” approach to inspections, the FDA instituted the Quality System Inspections Reengineering Team to develop a new approach to inspections of Medical Device establishments. The end result was the publication of the Guide to Inspections of Quality Systems – Quality Systems Inspection Technique (known as QSIT), which set forth a new front-end, top-down, Quality System oriented approach to inspections of Quality Systems. This new approach was based on “validation” rather than “verification”...quality assurance vs. quality control...sampling to establish a high confidence level based on statistical technique...a new “systems” methodology to conducting inspections, as opposed to the old haphazard, unselective approach. This new tactic (QSIT) integrated a top-down sampling evaluation of critical systems and subsystems within the Quality Management System, including but not limited to:

1. Management Controls
  - ✓ *Sr. Management’s commitment to quality*
  - ✓ *Quality Policy*
  - ✓ *Management review*
  - ✓ *Internal quality audits*
  - ✓ *Quality planning*
  - ✓ *Quality System procedures*
  - ✓ *Management Representative*
  - ✓ *Organizational structure, responsibility, authority, and resources);*



Discussion: QSIT puts a spotlight on Management, by starting and ending with interviews of Sr. Managers to ensure that they pay attention to and apply resources to Quality. The FDA will verify that Management provides adequate resources to meet QSR requirements, and ensure that they oversee compliance, review the system periodically, make adjustments to the system as needed, and keep the system running effectively.

2. Design Controls
  - ✓ *When are Design Controls Reviewed*
  - ✓ *IRB, IDE, 510(k), and PMA*
  - ✓ *Market Device*
  - ✓ *Design Control Procedures*
  - ✓ *Design Plan*
  - ✓ *Design Inputs*
  - ✓ *Acceptance Criteria*
  - ✓ *Design Outputs*
  - ✓ *Design Verification*
  - ✓ *Design Validation*
  - ✓ *Software Validation*
  - ✓ *Risk Assessment*
  - ✓ *Production Unit Validated*
  - ✓ *Design Change Control*
  - ✓ *Design Reviews*
  - ✓ *Design Transfer*

- ✓ *Design History File*
3. Corrective and Preventive Action (CAPA)
    - ✓ *CAPA procedures*
    - ✓ *Information sources identified*
    - ✓ *Information analyzed*
    - ✓ *Complete, accurate, and timely information*
    - ✓ *Statistical methods*
    - ✓ *Failure analysis vs. risk*
    - ✓ *Root Cause analysis*
    - ✓ *Remedial action (short term action to address the immediate problem)*
    - ✓ *Corrective Action to prevent recurrence (taken and documented)*
    - ✓ *Information Shared (Management Review)*
  4. Production and Process Controls (PAPC);
    - ✓ *Production and Process Control procedures*
    - ✓ *Environmental Controls and Monitoring*
    - ✓ *Facilities Controls*
    - ✓ *Device History Records*
    - ✓ *Nonconformance Control*
    - ✓ *Equipment installation (validation), maintenance, and calibration*
    - ✓ *Validation of Processes*
    - ✓ *Software Validation*
    - ✓ *Personnel Qualifications*
  5. Linkage to Other Subsystems in the QMS;
    - ✓ *Materials controls*
    - ✓ *Supplier selection, evaluation, and monitoring*
    - ✓ *Document and Data Controls*
    - ✓ *Records Management*
    - ✓ *Facility and Equipment Controls*
  6. Medical Device Reporting (MDR) - 21 CFR 803 (*satellite subsystem of CAPA*);
    - ✓ *MDR Procedures*
    - ✓ *MDR Files established*
    - ✓ *MDR Information complete*
    - ✓ *Adverse Reactions, including deaths, serious injury, and, malfunctions*
  7. Corrections and Removals (CAR) (*satellite subsystem of CAPA*);
    - ✓ *CAR procedures (i.e., Recalls)*
    - ✓ *CARs submitted*
    - ✓ *CARs completed*
    - ✓ *CAR File established*
  8. Medical Device Tracking (*satellite subsystem of CAPA*);
    - ✓ *Failure causes adverse health consequences (i.e., death, serious injury)*
    - ✓ *Obligation for traceability*
  9. Sampling
    - ✓ *FDA puts special emphasis on sampling Quality Records in an investigatory training program on implementing the QSIT.*

## **QSIT Sampling**



- ☘ **Sample**
- ☘ **Review**
- ☘ **Confirm**
- ☘ **Verify**

- ✓ *QSIT Handbook contains sampling tables to dictate how many samples to take for different confidence levels.*
- ✓ *Sampling for Confidence: Using Sampling Tables contained in the QSIT Manual, and reviewing a population of 35 randomly selected records (DHRs) of one device family, and finding only one deviation, the investigator can be 95% confident that less than, or equal to, only 15% of the set of records contains unrecognized nonconforming data points (test results).*
- ✓ *A key goal of the training is to instruct investigators on how to use record sampling to determine whether you comply with each of the quality subsystems.*
- ✓ *Investigators will select a sample of records to ensure that they reflect proper application of written procedures.*
- ✓ *FDA's position is that if quality systems are adequately established and implemented, occasional deviations in products or processes are less important because the systems will find and correct them.*

#### 10. Sterilization Process Controls (*satellite subsystem of PAPC*)

- ✓ *Sterilization Procedures*
- ✓ *Process validated*
- ✓ *Process controlled and monitored (i.e., dose audits)*
- ✓ *Control of Nonconformance*
- ✓ *Equipment installation (validation), maintenance, and calibration*
- ✓ *Software Validation*
- ✓ *Personnel qualified and trained*

Under the new QSIT, depending on the criticality of the device being manufactured (risk-based approach), and the compliance history of the manufacturer, FDA has defined three levels of inspection, much like that of an ISO registrar.

#### **Level One Inspection** (*Abbreviated Inspection*)

- This will be the standard inspection if you have passed previous inspections with a No Action Indicated (NAI) or Voluntary Action Indicated (VAI) classification.
- Each inspection will examine CAPA plus one additional subsystem.
- To help pick the second subsystem, investigators will examine changes in management and design control procedures, design change, and production/process control and production/process changes.
- Investigators will also review previous Establishment Inspection Reports (EIRs) to see which subsystems were covered in previous inspections, and to rotate inspection of subsystems.

#### **Level Two Inspection** (*Baseline Inspection*)

- All firms subject to the QS Regulation eventually will be subject to a comprehensive baseline inspection.
- Baseline Inspections over all four of the major Quality System subsystems to provide an overview of compliance.
  - ✓ Management Responsibility and Controls
  - ✓ Design Controls
  - ✓ Corrective and Preventive Action
  - ✓ Production and Process Controls
- As "district" resources allow, it is the goal of FDA to conduct a Level 2 Baseline Inspection at least once every 6 years.
- FDA will also check Medical Device Reporting (MDR) compliance, tracking of high-risk devices, corrections and removal procedures, and registration and listing.

### **Level Three Inspection** (*Compliance Follow-Up to Official Action Indicated*)

- Conducted to verify corrective actions in response to Official Action Indicated (OAI).
- If problems remain, the FDA investigator will collect “adequate evidence to support a possible regulatory action.”
- If adequate corrections were implemented, the inspection ends.

## **CLUES FROM QSIT – KNOWING WHEN AN INSPECTION IS IMMINENT**

The QSIT Manual may provide device manufacturers with significant clues as to how high they are on the FDA’s inspection priority list.

QSIT segregates the devices and diagnostics industry into two groups. “**Priority A**” firms make high-risk and Class III devices...and “**Priority B**” firms make Class I and II devices. Under QSIT, the following priority matrix is established:

### **Priority A firms:**

1. Never-inspected Class III device manufacturers
2. Firms receiving an Official Action Indicated (OAI) classification during the previous inspection
3. Establishments last inspected over two years ago, or with outstanding routine assignments
4. Other high-risk or Class III device establishments
5. Specification developers, re-packers, or re-labelers

### **Priority B firms:**

1. Never-inspected Class II device manufacturers
2. OAI follow-up of Class II or I firms
3. Class I/II firms with 2+ recalls in the past year
4. Manufacturers of Class II or I devices with recent increase in MDRs
5. Class II firms with 510(k)s in the past 2 years
6. Any other manufacturer of Class II devices
7. Class II specification developers or re-packagers/re-labelers
8. Never-inspected Class I device manufacturers
9. Manufacturers of Class I sterile devices
10. Any other manufacturer of Class I devices

Districts must schedule resources to inspect each year 50% of plants making high-risk devices and 40% of Class III. As more plants are found non-violative, and subsequently receive Level 1 Inspections, this frees agency resources to conduct inspections of Class II and I establishments.

“For Cause” inspections are separate from the QSIT program. They are conducted in the event that FDA receives information regarding a serious health risk presented by a company’s device. These “For Cause” Inspections are scheduled when the FDA learns of a recall, a consumer or health provider complaint, a malfunctioning device, or a Medical Device Report (MDR) via MedWatch.

Usually FDA gives five days notice of an inspection under its pre-announcement policy. At that time, it will ask you if you want to supply key manuals before the visit. The FDA generally will seek procedures that implement key sections of the QSR, such as Quality Manuals and Management Review procedures.

## **VALUE OF THE QSIT MANUAL IN COMPLIANCE GAP ANALYSIS AND INTERNAL AUDITS**

Adopting the QSIT approach to internal quality audits...evaluation of a sampling of an establishment’s activities to verify, by examination of objective evidence, the degree of compliance with those aspects of the quality program under review...in order to provide Management with executive responsibility a

high degree of confidence that they have appropriately allocated sufficient resources to the establishment and maintenance of the Quality Management System. The Management Review of the Quality System should include an evaluation of key metrics which might reveal to Sr. Management whether the Quality Management System is effectively implemented and managed and operating in a state of control. This review should include, but not be limited to, an evaluation of data collected from internal quality audits, documentation and investigation of deviations, nonconformances, corrective and preventive actions, complaints, evaluation and monitoring of suppliers, and other key quality indicators as required by Sr. Management. Under the QSIT approach, Sr. Management would be required to identify appropriate action to address trends which might lead to the manufacture of products which do not meet specification requirements.

The QSIT manual becomes an invaluable tool, along with the actual regulations themselves, in developing Audit Checklists to help you assess the degree of compliance of your Quality Management System and address the gaps identified from these Quality Audits.

## **USING QSIT TO PREPARE FOR FDA INSPECTIONS**

QSIT will be the framework behind your FDA Inspection...the “road map” utilized by the investigator in conducting the inspection. Since the overwhelming majority of field inspections performed by FDA inspectors are now done according to the Quality Systems Inspection Technique (QSIT), it is therefore imperative that all regulated companies have an in-depth knowledge of this systematic inspection process, to enable them to maintain a state of preparedness for FDA inspections. This author believes that the QSIT Manual should be studied and utilized by all personnel who may liaise with FDA during inspections, as well as by Senior Management who need to understand the methodologies used by the FDA during inspections.

Every device manufacturer should establish and maintain a procedure for managing FDA and other regulatory inspections. The QSIT Manual provides valuable guidance in the establishment of such a procedure.

Knowing and understanding the FDA’s approach to inspections, including the quality management subsystems that are likely to be the target of an FDA Inspection, should provide valuable assistance in identifying what inspectors look for during a QSIT Inspection.

Further, the QSIT Manual will help Sr. Management grasp the FDA’s statutory authority and give a thorough understanding of FDA’s enforcement actions.

## **QSIT AFTER THE FDA INSPECTION**

The QSIT Manual not only provides valuable assistance in preparing for FDA Inspections, and helpful counsel to personnel responsible for managing the FDA Inspection process, but also following the Inspection, the QSIT Manual conveys reliable guidance in understanding the FDA’s expectations. It is an indispensable instrument when preparing a response to FDA-483s and other regulatory action stipulated by the agency (e.g., classifications of voluntary action indicated; official action indicated, etc.), and for identifying and implementing an appropriate corrective action plan.

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About the author:



Jim Colyn is a Registered Lead Assessor of Quality Systems (RAB) with sixteen (16) years experience in Quality Systems Management. Jim is currently the President and principle consultant for **Jim Colyn and Associates Quality Consulting, LLC**, specializing in quality system development and compliance for the tissue industry. Before that, Jim was the head of Quality and Compliance for a large tissue processor, with responsibilities for ensuring overall compliance to Federal and State Regulations, and American Association of Tissue Bank (AATB) Standards for Tissue Banking. In that role, Jim and his staff of 30 quality professionals compiled an enviable regulatory compliance history.

Jim is a past Chairman of the AATB Education Committee, and is a member of the AATB Quality Taskforce, responsible for the Annual AATB Quality Workshop

He has led in the successful ISO 9001 registration of five (5) establishments in the oil service tools, plastics and elastomer industries, and ISO 13485 Registration of two (2) Human Tissue/Medical Device Organizations.

Jim is a frequent speaker with the American Association of Tissue Banks (AATB), Pharma Conference, American Organ Procurement Organizations (AOPO), Eye Bank Association of America, (EBAA), North American Transplant Coordinators Organization (NATCO), and the Center for Professional Advancement.