KEY2COMPLIANCE®
Compliance Training Network

TOOL FOR AUDITING

References to standards and GMP

FDA, QSIT Quality System Inspection Technique

FDA, Drug Manufacturing Inspections Guide

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160301

The requirements matrix is updated to the following versions:

21 CFR 210	Dec. 12, 2011
21 CFR 211	Mar. 20, 2013
21 CFR 820	Sep. 24, 2013
EU GMP, Part I	Mar. 01, 2015
EU GMP, Part I I	Sep. 01, 2014
EU GDP	Nov. 05, 2013
ISO 13485:2012	Mar. 01, 2015
ISO 9001:2015	Oct. 14, 2015

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Tool for auditing

This document is meant to serve as a support for the ones making quality audits in the pharmaceutical and medical device industry.

The quality systems referenced in this tool are:

- ISO 9001:2015 - Quality management systems
- ISO 13485:20116 - Medical devices - Quality management systems
- 21 CFR 820 - Quality System Regulation for Finished Devices (USA)
- 21 CFR 210 and 211 - CGMP for Finished Pharmaceuticals (USA)
- EU GMP Guidelines, Part I - Basic Requirements for Medicinal Products
- EU GMP Guidelines, Part II - Basic Requirements for Active Substances used as Starting Materials
- EU GDP Guide, 2013/C 343/01 - Good Distribution Practice of medicinal products for human use

An important characteristic of a good audit report is the inclusion of correct references to the audit criteria that where used. This tool facilitates the preparation of an audit checklist and also the report writing and has taken into account the similarities between requirements in all the relevant quality systems.

Preparations - You can create a rational checklist by picking out the relevant requirements from the matrix.

Report writing - You can easily correlate any findings to the requirements of the applicable standard / regulatory text.

Systematics - requirements that occur at several places in the text are highlighted and the requirements are listed on the basis of a modern quality systems perspective.

The tool includes three parts, see page 4.

Part 1 includes a requirement matrix that can be used in the preparation of checklists prior to the audit. It can also be used to identify cross-references between different quality systems, e.g. GMP and ISO standards.

On each spread, you will find a column with a header “Description of requirement” as well as references to the various standards / regulatory texts. The columns to the left of the description are related to requirements for medical devices and the columns to the right are related to pharmaceuticals. ISO 9001 that may be relevant for both medical devices and pharmaceuticals (i.e for certain subcontractors) is located to the far left.

Part 2 and 3 contain two inspection references from the FDA, one for medical devices and one for pharmaceuticals .

Contents

Part 1 Requirements matrix with references to standards and GMP
Requirements matrix with references between the requirements of ISO 9001, ISO 13485, 21 CFR 820 (Quality System Regulation for Finished Devices), 21 CFR 210/211 (cGMP for Finished Pharmaceuticals), the EU GMP Guide Part I (Pharmaceuticals), the EU Guide to GMP Part II (Pharmaceuticals, active starting materials) and the EU GDP guide for the distribution of medicinal products for human use.

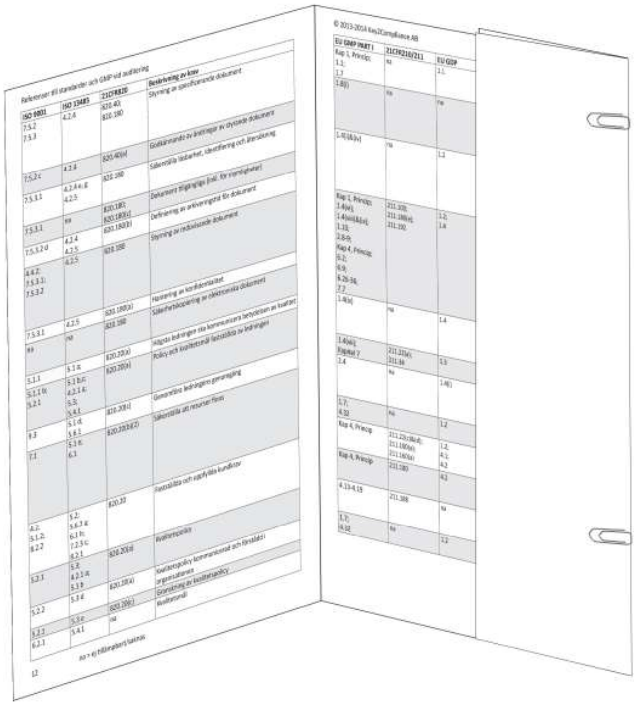
Part 2 QSIT – Quality System Inspection Techniques (FDA)
QSIT – Quality System Inspection Techniques – The inspection checklist used by the FDA in so-called systems inspection of establishments that are involved in development and manufacturing of medical devices. Note that this document not should be used to replace a comprehensive quality audit as it does not cover the entire quality system in detail. However, it can be very useful when preparing for FDA inspections and the questions can be used as inspiration for internal auditing.

Part 3 FDA Compliance Program, 7356.002 – Drug Manufacturing Inspections
FDA Compliance Program, 7356.002 – Drug Manufacturing Inspections is containing a description of how the FDA's normally carry out system inspections of pharmaceutical manufacturers. Page 25-27 also contains a summary of what is considered to be serious deficiency during an inspection.

Explanations of the matrix in Part 1

- Every other row is tinted for readability
- In all references the requirements are repeated to a certain extent.
  The matrix is sorted by the main paragraph in ISO 13485 but other references is also listed below in the same field.
- na = not applicable
- Notes field - this field can be used to add your own references, eg to internal procedures and documents or other specific notes.

  If you prefer not to make permanent notes in the document, you can attach a temporary sheet in the margin with clips or staples:



ISO 9001	ISO 13485	21CFR820	Description of requirement
4.4.1	4.1.1	820.5; 820.20(b)	Established Quality Management System
4.4.1 a, b	4.1.2 a,c; 4.2.2 c; 5.5.2 a; 7.1;	na	Identify processes, sequence and interaction
6.1	4.1.2 b; 4.1.5; 7.1; 7.3.3 c; 8.2.1	820.30(g)	Risk managment
4.4.1 c,d	4.1.3; 5.1 e; Ch. 6; 7.1 b;	na	Criteria, methods and resources necessary for control of processes
4.4.1 g	4.1.3.c; 5.6.3; 8.5.	820.100(a)(3)	Implement measures to achieve the planned results
4.4.1 g	4.1.3 c; 8.1; 8.2.5	820.100(a)(1)	Monitor,measure and analyze processes
8.4	4.1.5; 7.4.1	820.50	Control of outsourced processes
na	4.1.6; 7.5.6; 7.6	820.70(i)	Validation of software/automated processes
5.2.1 6.2.1	4.2.1 a; 5.1 b,c; 5.3; 5.4.1	820.20(a)	Documented quality policy and quality objectives
7.5.1	4.2.1 b; 4.2.2	820.20(e)	Quality manual
4.4.2	4.2.1 c,d; 4.2.2 b	820.5; 820.20(e); 820.40	Documented procedures
6.2; 8.2.2	4.2.3; 7.1 a; 7.3.3; 7.5.1 a	820.30(g); 820.70(a); 820.181	Documents defining product specifications and quality requirements including manufacturing, installation and service

 na = not applicable

EU GMP PART I	21CFR210/211	EU GMP PART II	EU GDP	Notes
Ch. 1, Principle ; 1.1; 1.7	na	2.11; 2.19; 17.30	1.1	
1.8(i)	na	2.12	na	
Ch. 1, Principle ; 1.3; 1.12-13 5.20-21; Ch. 8, Principle ;	na	2.20-21	1.5	
1.4(i)&(iv)	na	2.12	1.2	
1.4(ix)	na	11.15; 15.12	1.4	
Ch. 1, Principle ; 1.4(vi); 1.4(viii)&(ix); 1.10; 2.8-9; Ch. 4, Principle ; 6.2; 6.9; 6.26-36; 7.7	211.100; 211.180(e); 211.192	2.60; 6.71	1.2; 1.4	
1.4(vii); Ch. 7	211.22(a); 211.34	3.30; 16.10-16	1.3	
4.1; 4.29; Annex 11	211.68(b)	5.40-49	3.3.1	
2.4	na	2.19	1.4(i)	
1.7; 4.32	na	na	1.2	
Ch. 4, Principle	211.22(c)&(d); 211.100(a); 211.160(a)	2.12	1.2; 4.1; 4.2	
1.4(i); 4.13-4.19	211.100(a); 211.186	6.17	na	

Guide to Inspections of Quality Systems

Quality System Inspection Technique

QSIT

August 1999

This publication is a reproduction of “The Guide to Inspections of Quality Systems - QSIT ” from the Food and Drug Administration, ORA Inspectional References, published August 1999.

The text is complete and has not been altered from the original source.

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Review Procedures), Quality Manual, Quality Plan or equivalent documents to preview prior to the inspection. *The firm is not required to supply these documents*. The investigator should tell the firm that the preview of these procedural documents would facilitate the inspection. The documents would be returned at the time of the inspection. If you find deficiencies in these documents, you should request copies of the original documents after you initiate the inspection.

Getting Started

It is essential that the firm establishes and maintains a quality system that is appropriate for the specific medical device being manufactured and meets the requirements of the Quality System Regulation. The Management Representative has the responsibility to ensure that the requirements of the Quality System Regulation have been effectively established and maintained. Prior to your review of any subsystem, interview the Management Representative (or designee). The objective of this interview is to obtain an overall view of the subsystem as well as a feel for management's knowledge and understanding of the subsystem. An important linkage for this activity is Management Controls (820.20 Management Responsibility).

Management Controls Subsystem

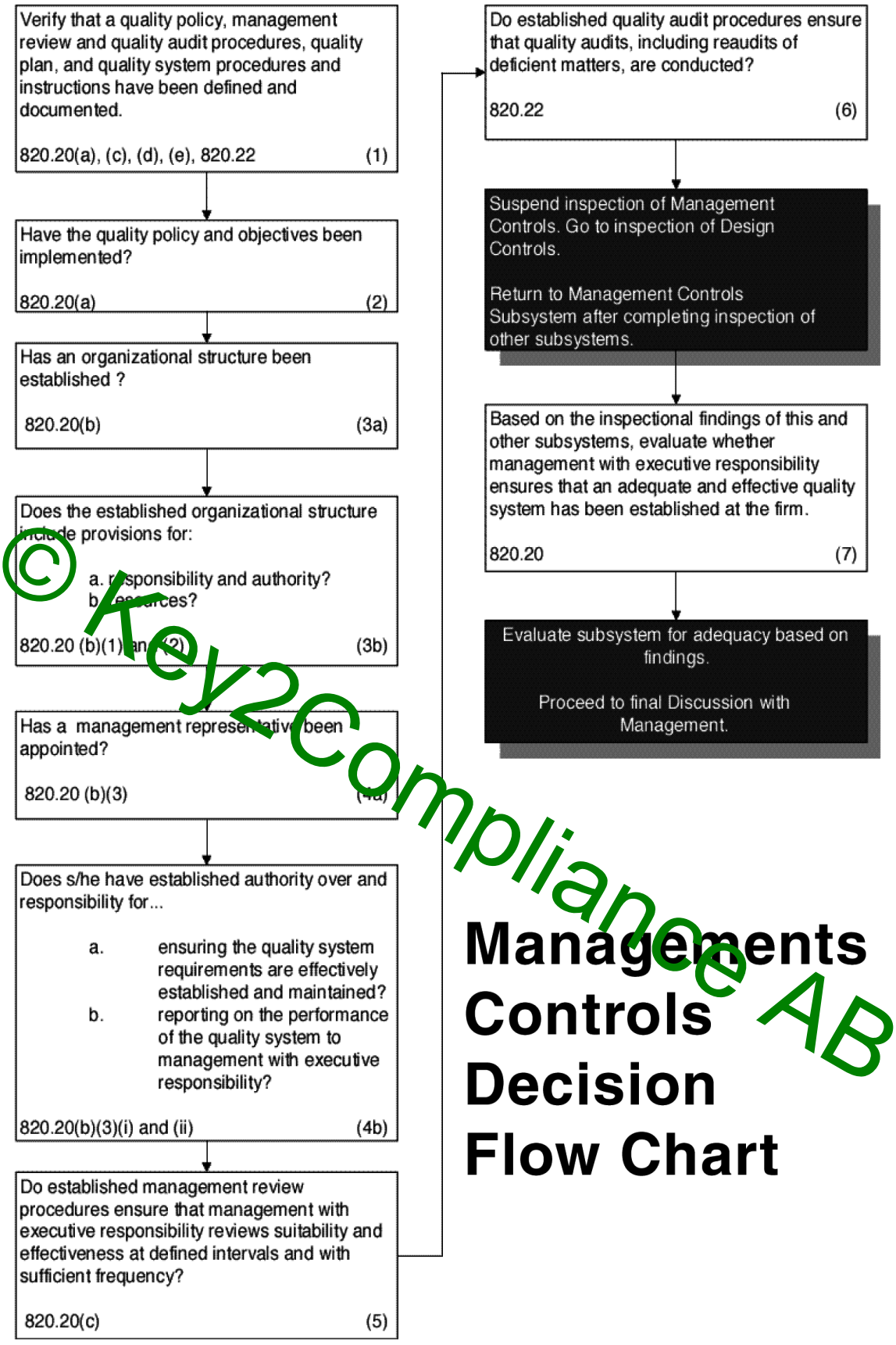
Management Controls

Inspectional Objectives

1. Verify that a quality policy, management review and quality audit procedures, quality plan, and quality system procedures and instructions have been defined and documented.
2. Verify that a quality policy and objectives have been implemented.
3. Review the firm's established organizational structure to confirm that it includes provisions for responsibilities, authorities and necessary resources.
4. Confirm that a management representative has been appointed. Evaluate the purview of the management representative.
5. Verify that management reviews, including a review of the suitability and effectiveness of the quality system, are being conducted.
6. Verify that quality audits, including re-audits of deficient matters, of the quality system are being conducted.

   At the conclusion of the inspection....

7. Evaluate whether management with executive responsibility ensures that an adequate and effective quality system has been established and maintained.



Managements Controls Decision Flow Chart

SUBJECT: DRUG MANUFACTURING INSPECTIONS	**IMPLEMENTATION DATE** 2/1/2002
	COMPLETION DATE Continuing

DATA REPORTING

PRODUCT CODES	**PRODUCT/ASSIGNMENT CODES**
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	Domestic / Foreign Inspections: 56002 56002A Sterile products manufacture 56002B Repackers and relabelers 56002C Radioactive drugs 56002E Compressed medical gases 56002F Bulk pharmaceutical chemicals

FIELD REPORTING REQUIREMENTS

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as OAI due to CGMP deficiencies as part of any regulatory action recommendation submitted to HFD-300. For all inspections that result in the issuance of a Warning Letter, forward an electronic copy of each letter to the Division of Manufacturing and Product Quality, Case Management and Guidance Branch (HFD-325). An e-mail account has been established to receive copies of Warning Letters. The account e-mail address is CDERCGMPWL.

This program provides guidance in evaluating compliance with CGMP requirements. As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency's new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS procedures. This includes filing OAI notifications and removing the notifications.

B. Inspection Planning

The Field will conduct drug manufacturing inspections and maintain profiles or other monitoring systems which will ensure that each drug firm receives biennial inspectional coverage, as provided for in the strategy.

The District Office is responsible for determining the depth of coverage given to each drug firm. CGMP inspectional coverage shall be sufficient to assess the state of compliance for each firm.

The frequency and depth of inspection should be determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products. When a system is inspected, the inspection of that system may be considered applicable to all products which use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities in manufacturing within CGMP requirements.

Review of NDA/ANDA files may assist in selecting significant drug processes for coverage in the various systems. Significant drug processes are those which utilize all the systems in the firm very broadly and/or which contain steps with unique or difficult manipulation in the performance of a step. Products posing special manufacturing features, e.g., low dose products, narrow therapeutic range drugs, combination drugs, modified release products, etc., and new products made under an approved drug application, should be considered first in selecting products for coverage.

The health significance of certain CGMP deviations may be lower when the drug product involved has no major systemic effect or no dosage limitations such as in products like calamine lotion or OTC medicated shampoos. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this systems approach will result in all profile classes being updated.

PART III - INSPECTIONAL

INVESTIGATIONAL OPERATIONS

A. General

Review and use the CGMPs for Finished Pharmaceuticals (21 CFR 210 and 211) to evaluate manufacturing processes. Use Guides to Inspection published by the Office of Regional Operations for information on technical applications in various manufacturing systems.

The investigator should conduct inspections according to the STRATEGY section in Part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should take place concurrently with inspection of an this system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach, one which allows the investigator to choose the inspection focus and depth appropriate for a specific firm, but also one which directs the performance and reporting on the inspection within a framework which will provide for a uniform level of CGMP assessment. Furthermore, this inspection approach will provide for fast communication and evaluation of findings.

Inspectional Observations noting CGMP deficiencies should be related to a requirement. Requirements for manufacture of drug products (dosage forms) are in the CGMP regulation and are amplified by policy in the Compliance Policy Guides, case precedents, etc. CGMP requirements apply to the manufacture of distributed prescription drug products, OTC drug products, approved products and products not requiring approval, as well as drug products used in clinical trials. The CGMP regulations are not direct requirements for manufacture of API's; the regulations should not be referenced as the basis for a GMP deficiency in the manufacture of Active Pharmaceutical Ingredients (APIs), but they are guidance for CGMP in API manufacture.

Guidance documents do not establish requirements. They state examples of ways to meet requirements. Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the CGMPs. Current Guides to Inspection and Guidance to Industry documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of CGMP systems.

Current inspectional observation policy as stated in the IOM says that the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this program. List observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. For those Districts utilizing Turbo EIR, a limited number of observations can be common to more than one system (e.g. organization and personnel including appropriate qualifications and training). In these instances, put the observation in the first system reported