KEY2COMPLIANCE®
Compliance Training Network

VERKTYG FÖR AUDITERING

Referenser till standarder och GMP

FDA, QSIT Quality System Inspection Technique

FDA, Drug Manufacturing Inspections Guide

1348se
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Notera även att innehållet baseras på standarder, lagtexter och guidedokument som löpande uppdateras. Kravmatrisen är uppdaterad till och med följande versioner:

21 CFR 210	12 Dec. 2011
21 CFR 211	20 Mar. 2013
21 CFR 820	24 Sep. 2013
EU GMP, Part I	01 Mar. 2015
EU GMP, Part II	01 Sep. 2014
EU GDP	05 Nov. 2013
ISO 13485:2016	01 Mar 2016
ISO9001:2015	14 okt. 2015

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Verktyg för auditering

Detta dokument är tänkt att fungera som ett stöd för den som gör auditering/revision av kvalitetssystem inom läkemedels- och medicinteknikbranschen.

De kvalitetssystem som refereras till i detta verktyg är:

- SS-EN ISO9001:2015 - Ledningssystem för kvalitet
- SS-EN ISO 13485:2016 - Medical devices - Quality management systems
- 21 CFR 820 - Quality System Regulation for Finished Devices (USA)
- 21 CFR 210/211 - CGMP for Finished Pharmaceuticals (USA)
- EU Guide för GMP, Del I - Läkemedel
- EU Guide för GMP, Del II - Läkemedel, aktiva substanser använda som startmaterial
- EU GDP Guide, 2013/C 343/01 - Distribution av humanläkemedel

En viktig egenskap i en bra audit/revisionsrapport är att kunna referera korrekt till de kriterier man auditerat/reviderat gentemot. Verktyget underlättar också förberedelsearbete och rapportskrivning samt har tagit hänsyn till de upprepningar av krav som finns i samtliga berörda kvalitetssystem.

Förberedelser – du kan skapa en rationell checklista genom att plocka ut relevanta krav ut matrisen

Rapportskrivning – du kan enkelt korrelera eventuella iakttagelser till krav i applicerbar standard/lagtext.

Systematik – krav som förekommer på flera ställen i respektive text är markerade och kraven är listade utifrån ett modernt kvalitetssystemperspektiv.

Verktyget innehåller 3 delar, se sid 4.

Del 1 innehåller en kravmatris som kan användas vid förberedelse av checklistor inför audit/revision. Den kan också användas för att identifiera korsreferenser mellan olika kvalitetssystem, t.ex. GMP och ISO-standarder.

På varje uppslag hittar du en kort beskrivning av kravet på vänster sida samt referenser till de olika standarderna/regeltexterna. Den vänstra sidan relaterar till krav på medicintekniska produkter och den högra sidan relaterar till läkemedel. ISO 9001 som kan vara relevant inom både medicinteknik och läkemedel (t.ex. vissa underleverantörer) ligger längst till vänster.

Del 2 och 3 innehåller två inspektionsreferenser från FDA, en för medicinteknik och en för läkemedel.

Innehåll

Del 1 Kravmatris med referenser till standarder och GMP
Kravmatris med referenser mellan krav i ISO 9001, ISO 13485, 21 CFR 820 (Quality System Regulation for Finished Devices), 21 CFR 210/211 (CGMP for Finished Pharmaceuticals), EU Guide för GMP Part I (Läkemedel) , EU Guide för GMP Part II (Läkemedel, aktiva startmaterial) samt EU GDP guide för distribution av humanläkemedel.

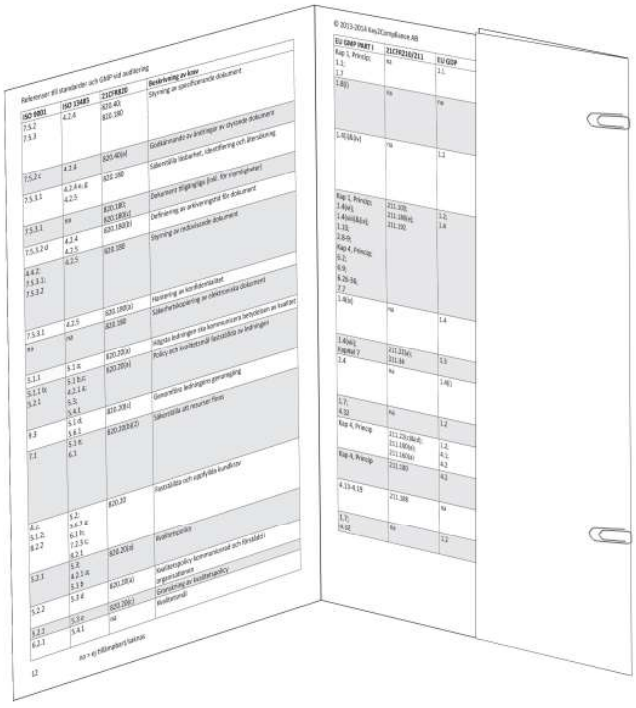
Del 2 QSIT – Quality System Inspection Techniques (FDA)
QSIT – Quality System Inspection Techniques – den inspektionschecklista som används av FDA vid så kallad systeminspektion av verksamheter som utvecklar och tillverkar Medicintekniska produkter. Observera att denna inte ska användas för att ersätta fullständig internaudit då den inte täcker hela kvalitetssystemet i detalj. Däremot kan den med fördel användas vid förberedelse för FDA-inspektioner och frågorna kan användas som inspiration vid internaudit.

Del 3 FDA Compliance Program, 7356.002 – Drug Manufacturing Inspections
FDA Compliance Program, 7356.002 – Drug Manufacturing Inspections som innehåller en beskrivning av hur FDAs systeminspektioner går till för läkemedelstillverkare. Sidan 25-27 innehåller också en sammanfattning av vad som anses vara allvarliga avvikelser i samband med en inspektion.

Förklaringar till matrisen i Del 1

- Varannan rad är tonad för läsbarhet
- I alla referenserna förekommer i större eller mindre utsträckning att krav upprepas. Matrisen är sorterad utifrån huvudparagrafen i ISO 13485 men övriga referenser i standarden finns också listade i respektive ruta.
- na = not applicable = ej tillämpbart/saknas
- Fält för egna noteringar – det här fältet kan du använda för att lägga in egna referenser, t.ex. till interna instruktioner och dokument eller andra specifika minnesanteckningar.

  Om du inte vill föra in uppgifter permanent utan vill kunna ändra så går det att fästa ett tillfälligt blad i marginalen.



ISO 9001	ISO 13485	21CFR820	Beskrivning av krav
4.4.1	4.1.1	820.5; 820.20(b)	Kvalitetsledningsystem upprättat
4.4.1 a, b	4.1.2 a,c; 4.2.2 c; 5.5.2 a; 7.1;	na	Identifiera processer, ordningsföljd och samverkan
6.1	4.1.2 b; 4.1.5; 7.1; 7.3.3 c; 8.2.1	820.30(g)	Riskhantering
4.4.1 c,d	4.1.3; 5.1 e; Kap 6; 7.1 b;	na	Kriterier, metoder och resurser för styrning av processer
4.4.1 g	4.1.3.c; 5.6.3; 8.5	820.100(a)(3)	Implementera åtgärder för att nå planerade resultat
4.4.1 g	4.1.3 d; 8.1; 8.2.5	820.100(a)(1)	Övervaka, mäta och analysera processer
8.4	4.1.5; 7.4.1	820.50	Hantering av utlagda processer
na	4.1.6; 7.5.6; 7.6	820.70(i)	Validering av programvara/mjukvara
5.2.1 6.2.1	4.2.1 a; 5.1 b,c; 5.3; 5.4.1	820.20(a)	Dokumenterad kvalitetspolicy och kvalitetsmål
7.5.1	4.2.1 b; 4.2.2	820.20(e)	Kvalitetsmanual
4.4.2	4.2.1 c,d; 4.2.2 b	820.5; 820.20(e); 820.40	Dokumenterade rutiner och specificerande dokument
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	Dokumenterade produkt- och kvalitetskrav inklusive tillverkningsprocess, installation och service

EU GMP PART I	21CFR210/211	EU GMP PART II	EU GDP	Egna noteringar
Kap 1, Princip; 1.1; 1.7	na	2.11; 2.19; 17.30	1.1	
1.8(i)	na	2.12	na	
Kap 1, Princip; 1.3; 1.12-13 5.20-21; Kap 8, Princip;	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	
Kap 1, Princip; 1.4(vi); 1.4(viii)&(ix); 1.10; 2.8-9; Kap 4, Princip; 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); Kapitel 7	211.22(a); 211.34	3.30; 16.10-16	1.3	
4.1; 4.29; Bilaga 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	
Kap 4, Princip	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

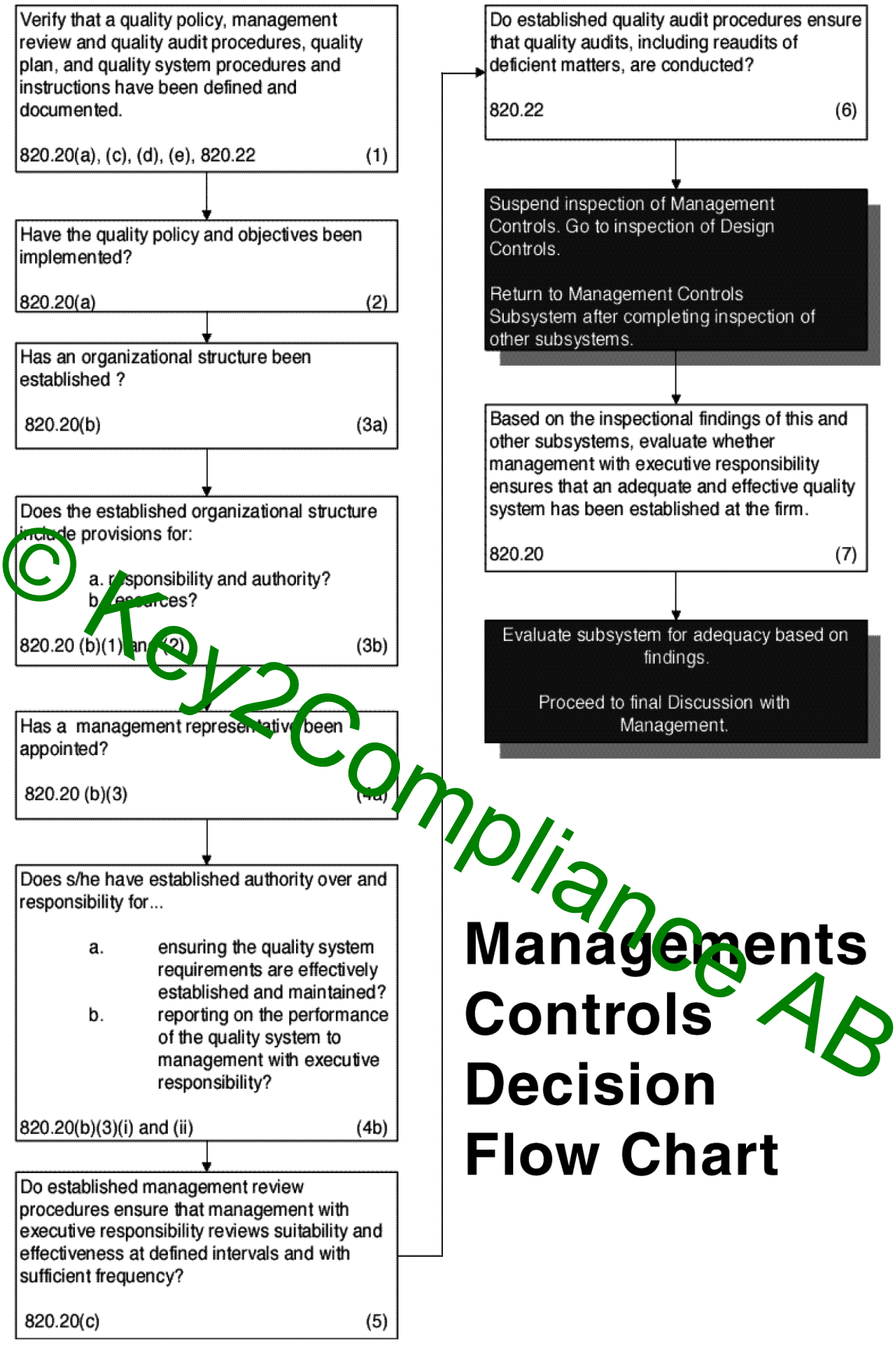
Management Controls

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