

## 18.H Questionnaire for preparing GMP-inspections

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### Here you will find answers to the following questions:

- What questions are typically asked during inspections based on current rules and regulations?
- Which reference documents (e.g. CFR, EU GMP Guideline, IPEC) comprise the GMP-requirement in question?

Supplier audits as well as inspections by the authorities are, in many regards, stressful situations for the auditee. There is generally a great deal hanging on the result of the inspection, whether it is an order from an important customer or approval for a new product. This means that all the members of staff involved in the inspection are under intense psychological pressure, which can make it difficult to present normally self-evident processes to the inspector in a comprehensible way and to answer questions fully and correctly.

Common concerns include the following:

- Will we be able to provide the correct answers or explanations to the questions posed in spite of general nervousness?
- Can we prove everything with documented evidence?
- Can we explain *that* (and how) our GMP or QA system works?
- Is our GMP status adequate?
- Will the staff make oversights because they feel watched or because they are scared to fail?
- Will the inspectors set “traps”?
- Will someone be caught out by their own reasoning because they want to make a particularly good impression?
- How will we stand internally after the inspection, e.g. with regard to other departments?

Only preparation can help to relieve these uncertainties and **self-inspection** can play an important element of this (chapter 18.E *Self-inspection*). The advantage of a self-inspection is that you can play with an open hand and any deficiencies that are recognized can be corrected immediately. The disadvantage is that an internal auditor is generally *too* familiar with the individual processes (even to the extent of wearing professional blinders) and only uses the internal terminology.

This only reflects the reality of an inspection by the authorities or a customer to a limited degree: here, the auditee may find himself confronted with terms or

questions that he had not considered in the same way. The generality of a question is often a worry: what is the meaning of “adequate water systems”? What is the inspector driving at when he asks about “suitable equipment” or “qualified personnel”? Even the terms used in the GMP rules and regulations do not always correspond to the expressions used in the company and can cause uncertainty: for example, if the “test procedures” are queried, does this mean the control procedures, the testing instructions, the testing plan, the analysis procedure, the IPC instructions, the calibration procedure or the stability plan? What does “process instruction” mean in a particular instance? The manufacturing formula in accordance with EU GMP, the processing instructions in accordance with EU GMP, the manufacturing description in accordance with CFR, the master production record in accordance with CFR, the batch production record in accordance with CRP or even an SOP?

Suppliers, in particular, who have generally structured their quality management system according to ISO 9000 or recently ISO 9001, use very different terms than the GMP inspector of a customer, for example. How do “quality planning”, “quality control”, “quality assurance” and “quality improvement” translate into GMP terms? Is “OOS” concerned with quality fault management or remedial actions? Can SPC and the concept of validation be made consistent?

For suppliers, an aggravating factor is that they are often confronted with GMP requirements that the pharmaceutical customer has been only too eager to pass on to the supplier. However, on closer inspection, many of these customer requirements cannot be traced back to legal requirements because they only relate to *pharmaceutical products* and not to the active pharmaceutical ingredient, excipient, packaging material or item of equipment.

To prepare for such general questions, an external consultant can be appointed to carry out a **mock inspection**. On the one hand, this allows the “real situation” to be tested and, on the other hand, it allows any weaknesses to be identified, which would not be obvious internally.

Alternatively or in addition to this, it is worth using checklists to deal with the questions that a GMP inspection may typically bring up. These can be considered carefully beforehand, e.g. which internal documents need to be kept at hand for a certain question – this will save some moments of panic during the inspection. Some US inspectors, in particular, like to use checklists, such as those in the Compliance Policy Guides or Compliance Policy Manual, to prepare themselves for the inspection. These sorts of checklists can also be used by the auditee as a useful preparatory aid.

However, when using **checklists** to prepare for an **inspection**, it must be taken into consideration, that:

- Simply filling in these lists can at best provide an initial overview. However, it does not replace the intensive challenge of the individual Quality System in place.
- Checklists can never be as comprehensive, exhaustive or specific enough to do justice to the situation at *every* (pharmaceutical, supplier, packaging, etc.)

company with all the various product ranges, different equipment pools and organizational differences.

- On the other hand, it will also include many questions that may not be applicable to the particular (pharmaceutical, supplier, packaging, etc.) company. However, it is still useful to be prepared for these questions so that you are not irritated during the actual inspection and can point out that a certain requirement only applies to pharmaceutical products, for example and not to active pharmaceutical ingredients, etc.
- Specific national legal requirements may have to be considered in addition.

A list of questions can also be useful for the auditor when preparing for the inspection to ensure that all the relevant aspects are discussed. Nevertheless, an inspection is not only about asking the right questions, but also assessing the corresponding answers. A checklist cannot take on this task. The checklist alone is often unsatisfactory for documenting the findings during the inspection (e.g. marking yes or no). More meaningful descriptions are very important in order to classify the deficiency (figure 18.D-10).

The following is a catalogue of typical general questions, which may be asked during an inspection. Chapter 18.I *Supplier qualification* contains a list of questions to be considered by manufacturers of active pharmaceutical ingredients when preparing for an inspection. The questions are referenced to the corresponding GMP regulations. In cases of doubt, the relevant original text can be quickly found.

A table divided up as follows is recommended for documenting the answers during an inspection:

Question	yes or fulfilled	partially fulfilled/ acceptable	partially fulfilled/not acceptable	no	Comment/ examined document
1.					
2.					
etc.					

The following regulations are used in the tables below as references:

- CFR: Code of Federal Regulations (US GMP regulations) see D.1.1.
- EU GMP Guideline: Guidelines to Good Manufacturing Practice of Medicinal Products for Human and Veterinary Use, see chapter C *EU GMP Guide*.
- IPEC: The IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, The International Pharmaceutical Excipients Council (IPEC) (2001)
- GMP Manual: Further information about this question in the GMP Manual in the chapter specified

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41. Storage and transport of pharmaceutical products  
42. Transport of pharmaceutical products

Typical audit questions	Assessment					GMP Manual chapter	CFR reference	EU GMP Guideline
	yes/met	partly met/accepted	partly met/not accepted	no				
<b>I General questions for manufacturers of medicinal products and active pharmaceutical ingredients (API)</b>								
<b>1. Opening discussion</b>						18.D.3.1		
1.1 Name and function of all persons present at the meeting								
1.2 Which operations are performed at the inspected company?								
1.2.1 Manufacturing of <ul style="list-style-type: none"> <li>• Drug substances (API)</li> <li>• Excipients</li> <li>• Packaging material</li> <li>• Drug product?</li> </ul>								
1.2.2 Packaging, Repackaging or labeling?								
1.2.3 Contract Manufacturing?								
1.2.4 Quality Control?								
1.2.5 Contract Analysis?								
1.2.6 Batch Release?								
1.2.7 Storage?								
1.2.8 Distribution?								
1.2.9 Import, Export, Trade?								
1.3 Have there been any changes with regard to the company's ownership or corporate identity?							601.12	
1.4 Have any additions or changes been made to the buildings or facilities which could affect the manufacture of the inspected product?							601.12	Annex 15: 4.3
1.5 Is a current building floor plan available?							601.12	Annex 15: 12a
<b>2. Application file for Marketing Authorization or Regulatory Approval</b>								
2.1 Do the actual manufacturing and testing procedures agree with the Marketing Authorization/Regulatory Filing?						14.J		1.1.vii + 1.2 + 1.3.viii 4.2 + 6.15 Annex 16: 3.1 + 8.1d
<b>3. Organization chart, personnel</b>								
3.1 Have there been changes of personnel which could have an effect on the product concerned?						2	601.12	

Typical audit questions	Assessment				GMP Manual chapter	CFR reference	EU GMP Guideline
	yes/met	partly met/accepted	partly met/not accepted	no			
3.2 Were the authorities informed when required?							
3.3 Is a documented quality assurance system in place?					1.B		Chapter 1 Part II: 2.11
• Is Quality risk assessment implemented as an integral part of the QA-System?							1.5 Annex 20
3.4 Is a current organization chart available?						601.12	2.2
3.5 Are there up-to-date detailed job descriptions for personnel who carry out GMP tasks?					2.A		2 Part II: 3.11
3.6 Who is responsible for manufacturing?					2.D.2		2.5
3.7 Does he/she have the necessary qualifications, knowledge and practical experience?					2.D.2	211.25	2.4c
3.8 Does he/she have sufficient skills/competences?					2.D.2		2.2
3.9 Is there a quality control unit in place?						211.22	6.1
• Are responsibilities and personnel assigned to quality control in conformance with regulatory requirements?					2.D.3		2.6, 6.1–6.2 Part II: 2.13, 2.22
3.10 Are raw materials, intermediates and/or final products approved by authorized persons as defined by regulatory authorities?					14.J.1.1	211.22d	1.1vii Part II: 2.14 + 2.22 Annex 16
3.11 Do they have the necessary qualifications, knowledge and practical experience?					14.J.1.1	211.25	2.4c, 6.1 Annex 16: 8.3 + 8.4
3.11.1 Is a "Qualified Person" designated?							2.3 Annex 16
3.11.2 Do they have sufficient skills/competences?					14.J.1.1		2.2, 6.1
3.11.3 Are the responsibilities and procedures of the Quality Control Unit established in written documentation?					2.D.3	211.22	1.1iii 2.6 + 2.7 Part II: 2.13 + 2.22
3.11.4 Are the heads of Production and Quality Control independent from each other?							2.3 6.1
3.11.5 Are there an adequate number of qualified personnel in the Quality Unit(s), manufacturing and packaging?					2.B.1	211.25c	1.2iii + v 1.3i 2.3, 2.8–2.12 Part II: 3.1
3.12 Is there a written training plan for employees?					2.C	211.25 a	2.9, 4.26 Part II: 3.12

Typical audit questions	Assessment				GMP Manual chapter	CFR reference	EU GMP Guideline
	yes/met	partly met/accepted	partly met/not accepted	no			
3.12.1 Does it include basic GMP principles as well as applicable regulations?						211.25 a	2.9
3.12.2 Does training include initial (new to the job) as well as ongoing (long-term) training?						211.25 a	2.6.viii, 2.9
3.12.3 Does it include technical, maintenance and cleaning personnel?							2.8 2.11
3.12.4 Does it address the specific requirements of each working area?						211.25a	2.10 + 2.20 Annex 1 Annex 3: 1 Annex 5: 1 Annex 6: 2 Annex 8: 1 Annex 11: 1 Annex 13: 3
3.13 Are there written records maintained of employee training?					2.C.8	211.25	2.9 Part II: 3.12
3.14 Is the effectiveness of training measures verified?							EEC-Directive: 7, Sec 4 2.9 Part II: 3.12
3.15 Are the qualifications of consultants checked?					1.H	211.34	Part II: 3.30
3.16 Is there a list of all consultants, their addresses, qualifications and the tasks they perform?						211.34	Part II: 3.31
3.17 Is there a written procedure in place for informing responsible management personnel of inspections, GMP deficiencies, product failures and of associated actions that may occur due to complaints or result in recalls?						211.180f	Part II: 2.18
<b>4. Buildings and infrastructure</b>							
4.1 Are all buildings and rooms of a suitable size, design and location to facilitate proper cleaning, maintenance and operations?					3.A 3.I	211.42 211.58 600.11	1.2iii Chapter 3, Part II: 41
• Are they qualified?							
4.2 Are buildings/rooms kept in an adequately clean, hygienic and tidy condition?					11.D	211.56a	3
4.3 Are separate or defined areas of sufficient size available for Incoming goods?					11.M.5.3	211.42c1	3.20 Part II: 4.14
4.3.1 Storage of raw materials?					11.M.5	211.42c1	3.18 + 5.7 Part II: 4.14
4.3.2 Storage of packaging materials?					13.A.5.4	211.42c1	1.2iii + 3.25
4.3.3 Weighing?					11.G		3.13