18.H Questionnaire for preparing GMP-inspections

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 chapter **D.1.1**.
- EU GMP Guideline: Guidelines to Good Manufacturing Practice of Medicinal Products for Human and Veterinary Use with a total of 18 appendices (labeled A 1–18), 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

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
Opening discussion			18.D.3.1
1. Name and function of all persons present at the meeting			
2. Which operations are performed in the company inspected?			
• Manufacturing of • Drug substances • Excipients • Packaging material • Drug product?			
• Packaging, Repackaging or labeling?			
• Contract Manufacture?			
• Quality Control?			
• Contract Analysis?			
• Batch Release?			
• Storage?			
• Distribution?			
• Import, Export, Trade?			
3. Have there been any changes with regard to the company's ownership or corporate identity?	601.12		
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: 43	
5. Is a current building floor plan available?	601.12	Annex 15: 12a	
Application file for marketing authorization			
6. Do the actual manufacturing and testing procedures correspond to the marketing authorization?		1.1vii + 1.2 + 1.3viii 4.2 + 6.15 Annex 16: 3.1 + 8.1d	

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 1 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
Organization chart, personnel			2
7. Have there been changes of personnel which could affect the product concerned?	601.12		
8. Were the authorities informed?			
9. Is a documented quality assurance system in place?		Chapter 1 Part II: 2.11	1
10. Is Quality risk assessment implemented as an integral part of the QA-System?		1.5 Annex 20	
11. Is a current organization chart available?	601.12	2.2	
12. Are there up-to-date detailed job descriptions for personnel who carry out GMP tasks?		2 Part II: 3.11	2.A
13. Who is responsible for manufacturing?		2.5	2.D.2
14. Does he/she have the necessary qualifications, knowledge and practical experience?	211.25	2.4c	2.D.2
15. Does he/she have sufficient skills/competences?		2.2	2.D.2
16. Is there a quality control unit in place?	211.22	6.1	
17. Who is responsible for quality control?		2.6, 6.1–6.2 Part II: 2.13 Part II: 2.22	2.D.3
18. Are intermediate and/or final products approved by authorized persons?	211.22d	1.1vii Part II: 2.14 + 2.22 Annex 16	14.J.1.1
19. Do they have the necessary qualifications, knowledge and practical experience?	211.25	2.4c , 6.1 Annex 16: 8.3 + 8.4	14.J.1.1
20. Is a "Qualified Person" designated?		2.3 Annex 16	
21. Do they have sufficient skills/competences?		2.2, 6.1	14.J.1.1

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 2 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
22. Are the responsibilities and procedures of the Quality Control Unit laid down in writing?	211.22	1.1iii 2.6 + 2.7 Part II: 2.13 + 2.22	2.D.3
23. Are the heads of Production and Quality Control independent from each other?		2.3 6.1	
24. Is there an adequate number of qualified personnel in manufacturing and packaging?	211.25c	1.2iii + v 1.3i 2.3, 2.8–2.12 Part II: 3.1	2.B.1
25. Is there a written training plan for employees?	211.25 a	2.9, 4.26 Part II: 3.12	2.C
• Does it include GMP regulations?	211.25 a	2.9	
• Does it include initial as well as ongoing training?	211.25 a	2.6.viii, 2.9	
• Does it include technical, maintenance and cleaning personnel?		2.8 2.11	
• 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	
26. Are there written records maintained of employee training?	211.25	2.9 Part II: 3.12	2.C.8
27. Is the effectiveness of training measures verified?		EEC-Directive: 7, Sec 4 2.9 Part II: 3.12	
28. Are the qualifications of consultants checked?	211.34	Part II: 3.30	1.C.10
29. Is there a list of all consultants, their ad dresses, qualifications and the tasks they perform?	211.34	Part II: 3.31	

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 3 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
30. Is there a procedure in place for informing all the responsible management personnel in the event of inspections by the authorities, severe GMP deficiencies, product failures and the associated actions (complaints, recalls)?	211.180f	Part II: 2.18	
Buildings and infrastructure			
31. Are all buildings and rooms of a suitable size, design and location to facilitate cleaning, maintenance and proper operations? Are they qualified?	211.42 211.58 600.11	1.2iii Chapter 3, Part II: 41	3.A 3.G
32. Are buildings/rooms kept in an adequately clean, hygienic and tidy condition?	211.56a	3	11.D
33. Are separate or defined areas of sufficient size available for Incoming goods?	211.42c1	3.20 Part II: 4.14	11.M.2.3
• Storage of raw materials?	211.42c1	3.18 + 5.7 Part II: 4.14	11.M.2
• Storage of packaging materials?	211.42c1	1.2iii + 3.25	13.A.5.4
• Weighing?		3.13	11.G
• Manufacture?	211.42c5	3.1, 3.8 Part II: 4.14	3.A 3.C
• Packaging?	211.42c6	3.15	3.A 3.C
• Quality control?	211.42c9	3.26–3.29 Part II: 4.14 + 4.16	3.A
• Storage of semi-finished or in-process materials?	211.42c4	1.2iii + 5.36	3.A
• Storage of finished products?	211.42c8	1.2iii 5.58 –5.60	11.M.2
• Storage of highly toxic medicinal products and narcotic substances?		3.24	11.M.2.6
34. Are the rooms used exclusively for their in tended purpose?		3.5 Part II: 4.43	

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 4 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
35. Is the material flow and the production process logical so as to minimise the risk of mixups or omission of manufacturing or testing steps?	211.42b + c	3.8 + 3.38 Part II: 4.13 Part II: 5.26	3.C 11.J
36. Are different tasks carried out in areas set up especially for that purpose and which are of an appropriate size and which have suitable equipment so as to prevent contamination and mix-up?	211.42	3.7–3.8 3.14 5.18–5.20 Part II: 4.13	11.J.1
37. Are measures taken to avoid cross-contamination?	211.42	Chapter 3 3.6, 3.8, 3.14, 3.15, 5.9, 5.18–5.20 Part II: 4.13 + 4.42	11.J
38. Is there adequate lighting and ventilation?	211.44	3.3, 3.12, 3.16 Part II: 4.21 + 4.5	3.A 3.B.4 3.F 3.H
39. Are there separate ventilation systems for highly potent active pharmaceutical ingredients?	211.46	3.6	21.D.1
40. Are the rooms fitted out so that the walls, ceilings and floors cannot emit particles into the room.	211. 42c10i	3.9	3.E
41. Are the rooms easy to clean and, if necessary, to disinfect?	211.42 211.56	3.9 3.14	3.B.5
42. Is the access to GMP-areas restricted to authorized personnel?	211.28c	3.5 5.16	3.A 3.B
43. Are Quality Control laboratories separated from production areas?		3.26–3.29 6.5 + 6.6 Part II: 4.16	3.A
44. Are the water systems adequate?	211.48	3.43 Part II: 4.3 + 4.34	5
45. Are waste and sewage disposed of safely and hygienically?	211.50 211.56a	3.11 Part II: 4.24 + 4.6	

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 5 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
Sanitation			
46. Is there a written sanitation program?	211.56	2.13, 3.2 4.26 Part II: 4.71	11.D
47. Does it contain responsibilities as well as cleaning intervals, techniques, equipment and materials?	211.56	3.2 Part II: 4.71	11.D
48. Is the sanitation program followed?	211.56	2.7 3.2	
49. Do the personnel practice good sanitation and health habits? Is direct contact with products avoided?	211.28b	2.13 2.17–18 Part II: 3.2	11.B
50. Is eating and smoking prohibited in the manufacturing rooms?	211.28b	2.17	11.B.3
51. Is clean hygienic and protective clothing worn that is suitable for the activity per formed?	211.28a	2.13 2.16 Part II: 3.21	11.B.1
52. Are members of staff who are suffering from an infectious illness or who have open wounds excluded from direct contact with products, in-process material, containers or raw material?	211.28d	2.14 Part II: 3.24	11.B.5
53. Are there written procedures on how to prevent microbiological contamination of medicinal products? Are they complied with?	211.113	5.10	11.B
54. Are the rooms clean?	211.56	3.2 Part II: 4.70	11.E 11.C.2
55. Are the rooms free from rodents, birds, in sects and other vermin?	211.56c	3.4 Part II: 4.72	11.M.3.2
56. Are there adequate clean toilet and washing facilities easily accessible from working areas?	211.52	2.19, 3.31 Part II: 4.15	3.A
57. Are there sufficient changing rooms?		3.31	3.C.2
58. Is there a written environmental monitoring plan?	211. 42c10iv	2.7 4.26	11.E 12.G

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 6 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
59. Are there records available?		4.26	11.E 12.G
60. Are the measures carried out documented?		4.26	11.E 12.G
Apparatus and equipment			
61. Is the design, installation and location of all apparatus suitable for the intended purpose?	211.63 211.65	3.34–3.39 Annex 9: 2 Part II: 5.10	4.B.2 4.E.1 6.D
62. Is thorough cleaning facilitated?	211.67a	3.36 Annex 9: 1 Part II: 5.10	4.B.2 8.B 11.J.2
63. Are tanks, containers, pipes and pumps designed and installed in such a way that they can be easily cleaned and disinfected without dead-legs and poorly accessible points?		3.10 Annex 9: 2 Part II: 4.23	4.I 11.J.2 8.B
64. Are sufficient measures carried out during the manufacturing operation to prevent contamination of the medicinal products and their containers (including the pack aging)?	211.42b 211.65b	3.38	11.J
65. Is the equipment constructed in a way, that surfaces which come into contact with products do not alter the quality of the products?	211.65	3.39 Annex 9: 3 Part II: 5.11 + 5.14	4.B.1 4.L
66. Is defective equipment removed from the production or control area or clearly labeled as defective?	211. 160b4	3.44	11.J
67. Are there up-to-date drawings available of the equipment and installations?		Part II: 5.16	4.F
68. Are there written plans available for DQ, IQ, OQ, PQ and requalification?	211.68	4.26 Annex 15	6.D, 6.E, 6.F, 6.G
69. Are the qualification plans based on documented quality risk assessments?		1.5 A20	6.B.6

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 7 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
70. Are there specifications available and writ ten protocols of regular calibration of measuring, weighing, recording and control equipment?	211.68 211. 160b4 211.194d	3.41 Annex 15: 19 Part II: 5.3	4.G
71. Are there written procedures on how to clean and maintain the equipment?	211.67	2.5iv + 2.6vi 3.36, 3.43 Part II: 5.2	8.B.2
• Are they sufficiently detailed?			
• Do they contain information on cleaning intervals?			
• Do they specify, when cleaning has to be repeated, in case equipment has not been used for some time?			
72. Are they complied with?	211.67	3.36	
73. Are cleaning, maintenance and use of equipment documented, e.g. in equipment logs?	211.182	4.28 Part II: 6.2	4.F.4
74. Have the cleaning processes been validated?		Annex 15: 36	8
75. Who performes equipment cleaning?		2.8 + 2.9	
76. Is this staff specially trained to perform cleaning correctly?		2.8 + 2.11	2.C.4
77. Who performes maintenance of equipment?		2.8 + 2.9	
78. Is this staff specially trained in GMP issues?		2.8 + 2.11	2.C.4
79. Are there written operating instructions for manufacturing and testing equipment?		4.27	
80. Are logbooks kept (for major equipment)?	211.67c 211.182	4.28 + 4.29	4.F.4
81. Are all the major apparatus and facilities identified and is this information included in batch records?	211.105b	4.17f 4.18f	11.H.2 15.C
82. Are there records available on the cleaning and usage of the equipment?	211.67c 211.182	4.28, 4.29 Part II: 6.2	15.C

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 8 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
83. Are there adequate controls for the computers and associated systems to ensure that changes to the (master) specifications can only be made by authorized personnel?	211.68	4.9 Part II: 5.4	9
84. Is the data input and output checked for accuracy?	211.68	4.9 Part II: 5.45	9
85. Are files backed up?	211.68	Annex 11: 13	9
86. Are fiber-releasing filters used for liquid filtration? If so, are additional non-fiber-releasing filters used as required?	211.72		12.C.4
Control of raw materials and containers			
87. Is there a list available of all raw material suppliers?	680.1	Part II: 7.1	
88. How often is this list updated?	680.1		
89. Have the suppliers been suitably qualified? How?		1.1iv 5.26 + 7.3 Annex 8: 3 Part II: 7.11 and 7.31	18.G 18.I
90. Are there written contracts with suppliers, addressing GMP aspects?		1.1iv	18.I
91. Are there supplier lists for all incoming raw materials, including those that are rejected?		Part II: 7.11	11.M.4
92. Are there records for all raw materials?	211.180b	4.19	11.M.4
93. Do they contain details of their origin?		5.26, 4.20d Part II: 7.13 Annex 2: 25	11.M.4
94. Do they contain the date of receipt?		4.20c	11.M.4
95. Are there written instructions which describe the following procedures for raw materials and medicinal product containers	211.80 211.82	4.19–4.21, 5.2 Part II: 7.10, 7.33, 7.4	

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 9 of 48)

Typical audit questions	CFR reference	EU GMP Guideline	GMP Manual chapter
• receipt			11.M.4 21.G.2
• identification			11.M.5 21.G.3
• storage			11.M 21.G.4
• handling			
• sampling			14.A 21.G.3
• analysis			14 21.G.3
• release or rejection?			14.J
96. Are these directions followed?	211.80	4.19– 4.21	
97. Is each container identified with a unique code when it is received?	211.80d	4.21, 5.3 Part II: 7.24	11.H.1 11.M.5
98. Is there a status identification for each batch?	211.80d	5.29	11.H.1
99. Are there adequate quarantine procedures in place?	211.82b 211.110d2 11.142	4.21 5.2, 5.5, 5.58 Part II: 4.14, 7.10, 7.44, 10.11	11.H.1 11.M.2.5
100. Are they complied with?	211.82	4.21	
101. Are all materials fully and satisfactorily assessed before they are approved or used?	211.84a	1.3 Part II: 2.17 + 7.20 Annex 2: 25	14.J
102. Does the manufacturer rely on the suppliers' certificates? If yes, how does the manufacturer "validate" the suppliers' test results?	211.84d2 + d3	5.26 Part II: 7.30 Annex 8: 3	17.B 18.G

Figure 18.H-1 Typical questions which might be put during a GMP inspection (section 10 of 48)