國際間公佈GMP相關Q&A的說明

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1. 本講題係提供以Q&A發佈之GMP相關為主的國際新資訊。
2. 各主題資訊的出處包括：EMA 、FDA 、 EC 、 PIC/S、ICH與USP等。
3. 本講題僅提供各別主題之Q&A中Q（問題）的書面資料，其完整Q&A可自各別資訊出處取得。

1. EMA	Questions and answers on production of water for injections by non-distillation methods–reverse osmosis and biofilms and control strategies （Draft）＜10 June 2016＞
2. FDA	Data Integrity and Compliance With CGMP Guidance for Industry ＜April 2016＞
3. EMA	Data integrity，GMP/GDP compliance-Q&A Good Manufacturing Practice (GMP) ＜August 2016＞
4. EUROPEAN COMMISSION	IMPORTATION OF ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE QUESTIONS AND ANSWERS VERSION 7 ＜June 2016＞
5. FDA	Questions and Answers on Current Good Manufacturing Practices for Drugs＜2015＞
6. FDA	Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Questions and Answers＜May 2014＞
7. ICH	Q7 Guideline , Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients，Questions and Answers＜10 June 2015＞
USP	Water for Pharmaceutical Purposes＜1231＞【USP 2S (USP39)】
EMA	Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container＜Draft＞ ＜11 April 2016＞
＜Data Integrity＞新資訊（非Q&A,未納入本講題中）：	
WHO	GUIDANCE ON GOOD DATA AND RECORD MANAGEMENT PRACTICES Annex 5, WHO Technical Report Series 996 ＜2016＞
PIC/S	GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS＜10 August 2016＞
MHRA	MHRA GxP Data Integrity Definitions and Guidance for Industry Draft version for consultation ＜July 2016＞

1. EMA

Questions and answers on production of water for injections by non-distillation methods–reverse osmosis and biofilms and control strategies （Draft）

10 June 2016
EMA/INS/GMP/489331/2016
GMP/GDP Inspectors Working Group

Water for Injection USP

Definition

Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.

It is prepared from water complying with the U.S. Environmental Protection Agency National Drinking Water Regulations or with the drinking water of the European Union or of Japan or with World Health Organizations' Guideline for Drinking Water Quality. It contains no added substance.

歐洲藥典：Water for injections in bulk（EP）

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets.

The correct maintenance of the apparatus is essential. The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected.

In order to ensure the appropriate quality of the water, validated procedures and in-process-monitoring of the electrical conductivity and regular microbial monitoring are applied.

Water for injections in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

Part I

Production of WFI by non-distillation methods – reverse osmosis

< Part I > 問題

1. **The monograph requires that notice is given to the supervisory authority of the manufacturer before implementation. Who is the supervisory authority?**
2. **What are the main concerns around the use of reverse osmosis to manufacture WFI?**
3. **What are the main elements that should be considered in the design of such a system?**
4. **What approach should be considered for the qualification of such a system?**
5. **What type of sampling regime should be employed during qualification and during operation?**
6. **What testing should be employed during initial qualification and routine operation sampling?**
7. **What are the expectations for preventative maintenance on RO systems used for the production of WFI?**

＜問題＞

2. What are the main concerns around the use of reverse osmosis to manufacture WFI?

＜答案＞

The main concerns around the use of non-distillation methods – Reverse Osmosis, for the manufacture of WFI relate to the microbiological quality of the water produced as well as the control mechanisms in place to minimise the risks associated with microbiological proliferation and/ or by-products throughout such a system which is not easily detected.

RO systems typically operate at ambient temperatures and as such offer an ideal environment for the formation of a biofilm.

Biofilms are notoriously difficult to remove, because they protect flora contained within against the action of shear forces and disinfection chemicals. In addition, incompletely removed biofilms lead to a rapid regrowth and proliferation as well as increasing the likelihood of microbiological by-products throughout a system.

Part II

Biofilms and control strategies

Part II ＜問題＞

1. **What is a biofilm?**
2. **What approach should be taken to maintain control over systems which can be affected by biofilms?**
3. **What is a control strategy in the context of biofilm and contamination control?**
4. **If a biofilm exists what steps can be taken to eradicate or remove it?**
5. **What specific agents can be used as part of a control strategy?**
6. **Are there any additional measures which should be considered in order to increase the probability of detecting the presence of biofilms?**

＜問題＞

4. If a biofilm exists what steps can be taken to eradicate or remove it?

＜答案＞

The approach is both chemical and physical removal. When sanitising systems in this manner it is important to ensure that the systems are in recirculation mode and the sanitising agents utilised are not introduced into a system and left to exert their mode of action in a passive mechanism. Any approach to biofilm removal needs to be an active in operational strategy.

Use of chemical sanitising agents should be incorporated into a control strategy. While the utilisation of a hot water flush through systems is considered somewhat acceptable in order to minimise the planktonic contaminants existing within a system, it is known not have a significant effect on biofilms, which typically do not exist in a planktonic form, but usually in a sessile or attached form.

＜問題＞

4. If a biofilm exists what steps can be taken to eradicate or remove it?（續）

＜答案＞

The ideal mode of action of chemical sanitising agents in the context of biofilm is to both penetrate and provide the appropriate kill to the organisms in question.

Appropriate removal of cellular debris should also be considered, as excessive debris can result in increased levels of endotoxin/exotoxin etc. existing within the system.

Frequent, rotation of disinfectants & detergents and inclusion of sporicidal agents should be considered as part of a robust strategy.

＜問題＞

4. If a biofilm exists what steps can be taken to eradicate or remove it?（續）

It should be noted that once a biofilm has been established it may be difficult to remove even using the methods above. Any biofilm removal should be followed by a period of intense monitoring before returning the system to use to ensure that the biofilm has been effectively removed.

A robust preventative maintenance programme is essential in order to maintain equipment and premises to a standard that will not add significant risk from a contamination viewpoint. Consider regular inspection of utilities, process equipment and transfer lines for obvious signs of deterioration－O-rings, gaskets, seals －regular inspection and replacement.

2. FDA

Data Integrity and Compliance With CGMP Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

1. Please clarify the following terms as they relate to CGMP records：
- a. What is “data integrity”?
- b. What is “metadata”?
- c. What is an “audit trail”?
- d. How does FDA use the terms “static” and “dynamic” as they relate to record formats?
- e. How does FDA use the term “backup” in § 211.68(b)?
- f. What are the “systems” in “computer or related systems” in § 211.68?

2. When is it permissible to exclude CGMP data from decision making?

3. Does each workflow on our computer system need to be validated?

＜續＞

4. How should access to CGMP computer systems be restricted?
5. Why is FDA concerned with the use of shared login accounts for computer systems?
6. How should blank forms be controlled?
7. How often should audit trails be reviewed?
8. Who should review audit trails?
9. Can electronic copies be used as accurate reproductions of paper or electronic records?
10. Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?
11. Can electronic signatures be used instead of handwritten signatures for master production and control records（MPCR）?
12. When does electronic data become a CGMP record?

＜續＞

13. Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?
14. Is it acceptable to only save the final results from reprocessed laboratory chromatography?
15. Can an internal tip regarding a quality issue, such as potential data falsification be handled informally outside of the documented CGMP quality system?
16. Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?
17. Is the FDA investigator allowed to look at my electronic records?
18. How does FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?

＜問題＞

1. Please clarify the following terms as they relate to CGMP records:
a. What is "data integrity"?

＜答案＞

For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data.

Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

＜問題＞

1. Please clarify the following terms as they relate to CGMP records:（續）
b. What is "metadata"?

＜答案＞

Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data.

Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. For example, the number "23" is meaningless without metadata, such as an indication of the unit "mg."

＜問題＞

1. Please clarify the following terms as they relate to CGMP records:（續）

b. What is “metadata”?

＜答案＞

Among other things, metadata for a particular piece of data could include a date/time stamp for when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, audit trails, etc.

Data should be maintained throughout the record’s retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194).

The relationships between data and their metadata should be preserved in a secure and traceable manner.

＜問題＞

4. How should access to CGMP computer systems be restricted?

＜答案＞

You must exercise appropriate controls to assure that changes to computerized MPCRs, or other records, or input of laboratory data into computerized records, can be made only by authorized personnel (§ 211.68(b)). FDA recommends that you restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data).

FDA suggests that the system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content. To assist in controlling access, FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.

＜問題＞

4. How should access to CGMP computer systems be restricted?（續）

＜答案＞（續）

If these independent security role assignments are not practical for small operations or facilities with few employees, such as PET or medical gas facilities, FDA recommends alternate control strategies be implemented.

For example, in the rare instance that the same person is required to hold the system administrator role and to be responsible for the content of the records, FDA suggests having a second person review settings and content. If second-person review is not possible, the Agency recommends that the person recheck settings and his or her own work.

3. EMA

Data integrity
GMP/GDP compliance-Q&A
Good Manufacturing Practice (GMP)

August 2016
European Medicines Agency

＜問題＞

1. How can data risk be assessed?
2. How can data criticality be assessed?
3. **What does 'Data Lifecycle' refer to?**
4. Why is **'Data lifecycle'** management important to ensure effective data integrity measures?
5. What should be considered when reviewing the 'Data lifecycle'?
6. '**Data lifecycle**': What risks should be considered when assessing the generating and recording of data?
7. '**Data lifecycle**': What risks should be considered when assessing the processing data into usable information?
8. **'Data lifecycle**': What risks should be considered when checking the completeness and accuracy of reported data and processed information?

＜問題＞（續）

9. '**Data lifecycle**': What risks should be considered when data (or results) are used to make a decision?
10. '**Data lifecycle**': What risks should be considered when retaining and retrieving data to protect it from loss or unauthorised amendment?
11. **'Data lifecycle**': What risks should be considered when retiring or disposal of data in a controlled manner at the end of its life?
12. Is it required by the EU GMP to implement a specific procedure for data integrity?
13. **How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4?**

＜問題＞（續）

14. How should the company design and control their paper documentation system to prevent the unauthorised re-creation of GMP data?
15. What controls should be in place to ensure original electronic data is preserved?
16. Why is it important to review electronic data?
17. Is a risk-based review of electronic data acceptable?
18. What are the expectations for the self-inspection program related to data integrity?
19. What are my company's responsibilities relating to data integrity for GMP activities contracted out to another company?
20. How can a recipient (contract giver) build confidence in the validity of documents such as Certificate of Analysis (CoA) provided by a supplier (contract acceptor)?

＜問題＞（續）

21. What are the expectations in relation to contract calibration service providers who conduct calibrations on-site and/or off-site? Are audits of these companies premises required?
22. What is expected of my company in the event that one of my approved contractors (e.g. active substance manufacturer, finished product manufacturer, quality control laboratory etc.) is issued with a warning letter/statement of non-compliance concerning data integrity, from a regulatory authority?
23. Where does my company's responsibility begin and end in relation to data integrity aspects of the supply chain for medicinal products?

＜問題＞

3. What does 'Data Lifecycle' refer to?

＜答案＞

'Data lifecycle' refers to how data is generated, processed, reported, checked, used for decision-making, stored and finally discarded at the end of the retention period.

Data relating to a product or process may cross various boundaries within the lifecycle, for example:

- IT systems
  - Quality system applications
  - Production
  - Analytical
  - Stock management systems
  - Data storage (back-up and archival)
- Organisational
  - Internal (e.g. between production, QC and QA)
  - External (e.g. between contract givers and acceptors)
  - Cloud-based applications and storage

＜問題＞

13. How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substance and dosage forms published in Eudralex volume 4?

＜答案＞

The main regulatory expectation for data integrity is to comply with the requirement of ALCOA principles. The table below provide for each ALCOA principle the link to EU GMP references (Part I, Part II and Annex 11):

	Basic Requirements for Medicinal Products (Part I): Chapter 4(1) / Chapter 6(2)	Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 6(3) / Chapter 5(4)	Annex 11 (Computerised System)
Attributable (data can be assigned to the individual performing the task)	**[4.20, c & f], [4.21, c & i],[4.29, e]**	**[6.14], [6.18], [6.52]**	**[2], [12.4], [15]**
Legible (data can be read by eye or electronically and retained in a permanent format)	**[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]**	**[5.43] [6.11], [6.14], [6.15], [6.50]**	**[7.1], [9], [10], [17]**
Contemporaneous (data is created at the time the activity is performed)	**[4.8]**	**[6.14]**	**[12.4], [14]**
Original (data is in the same format as it was initially generated, or as a 'verified copy', which retains content and meaning)	**[4.9], [4.27], [Paragraph "Record"]**	**[6.14], [6.15], [6.16]**	**[8.2], [9]**
Accurate (data is true / reflective of the activity or measurement performed)	**[4.1], [6.17]**	**[5.40], [5.45], [6.6]**	**[Paragraph "Principles"],[5], [6], [10], [11]**

1Chapter 4 (Part I): Documentation
2Chapter 6 (Part I): Quality Control
3Chapter 5 (Part II): Process equipment (Computerized system)
4Chapter 6 (Part II): Process equipment

＜問題＞

22.What is expected of my company in the event that one of my approved contractors (e.g. active substance manufacturer, finished product manufacturer, quality control laboratory etc.) is issued with a warning letter/statement of non-compliance concerning data integrity, from a regulatory authority?

＜答案＞

It is considered that the company should evaluate the risk to its products manufactured/released using the principles of quality risk management. Risk assessments should be made available to Inspectors, on request.

Depending on the outcome of the risk assessment, appropriate action should be taken which may entail delisting the contractor from the approved contractor list. In the event that abnormal disruption in supply may result from a contractor compliance situation, relevant regulatory authorities should be consulted in this regard.

＜Data Integrity＞新資訊還有：
（1）MHRA
MHRA GxP Data Integrity Definitions and Guidance for Industry **Draft version for consultation** **July 2016** **Medicines and Healthcare products Regulatory Agency** **GOV.UK**
（2）WHO
GUIDANCE ON GOOD DATA AND RECORD MANAGEMENT PRACTICES **Annex 5,** **WHO Technical Report Series 996** **2016**

（3）PIC/S
GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS
PHARMACEUTICAL INSPECTION CONVENTION **PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME** **PI 041 -1 (Draft 2)** **10 August 2016**

ALCOA原則與PIC/S 相關規範之條項的連結

ALCOA原則 ALCOA principle	PIC/S藥品優良製造規範指引PE009 (第 I部) PIC/S Guide to Good Manufacturing Practice for Medicinal products, PE009 (Part I):	PIC/S藥品優良製造規範指引PE009 (第II部) PIC/S Guide to Good Manufacturing Practice for Medicinal products, PE009 (Part II):	附則11（電腦化系統） Annex 11 (Computerised Systems)	PIC/S藥品優良運銷規範指引PE011 PIC/S Guide to Good Distribution Practice for Medicinal products, PE011:
可歸屬的 Attributable	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]	[4.2.4], [4.2.5]
易讀的 Legible	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]	[4.2.3], [4.2.9]
同一時間的 Contem-poraneous	[4.8]	[6.14]	[12.4], [14]	[4.1], [4.2.9]
原始的 Original	[4.9], [4.27] [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]	[4.2.5]
準確的 Accurate	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"] [5], [6], [10],[11]	[4.2.3]

4. EUROPEAN COMMISSION
IMPORTATION OF ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE QUESTIONS AND ANSWERS **VERSION 7**
June 2016 **EUROPEAN COMMISSION** **DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY** **Health systems and products** **Medicinal products–quality, safety and efficacy**

＜問題＞

1. WHEN DO THE NEW RULES FOR THE WRITTEN CONFIRMATION APPLY?

2. DO THE RULES ON THE WRITTEN CONFIRMATION ALSO APPLY TO BLOOD PLASMA?

3. DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND DEVELOPMENT TRIALS?

4. DO THE RULES ON THE WRITTEN CONFIRMATION APPLY TO ACTIVE SUBSTANCES WHICH ARE BROUGHT INTO THE EU WITHOUT BEING IMPORTED ('INTRODUCED' ACTIVE SUBSTANCES)? AN EXAMPLE IS THE INTRODUCTION OF AN ACTIVE SUBSTANCE WHICH IS SUBSEQUENTLY EXPORTED

5. WHAT IF, AT THE TIME OF EXPORT OF AN ACTIVE SUBSTANCE TO THE EU, IT IS NOT KNOWN WHETHER THE ACTIVE SUBSTANCE IS USED IN A MEDICINAL PRODUCT FOR HUMAN USE OR NOT?

＜問題＞

6. IS THE WRITTEN CONFIRMATION EXPECTED TO CONFIRM COMPLIANCE WITH EU-RULES?

7. IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS FOR MANUFACTURING OF ACTIVE SUBSTANCES ARE THE GOOD MANUFACTURING PRACTICES FOR ACTIVE SUBSTANCES OF THE WORLD HEALTH ORGANISATION (WHO) – FORTY-FOURTH TECHNICAL REPORT, NO. 957, 2010, ANNEX 2. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?

8. IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS ARE ICH Q7. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?

9. DOES THE WRITTEN CONFIRMATION HAVE TO BE ISSUED BY A CENTRAL, REGIONAL OR LOCAL AUTHORITY?

＜問題＞

10. DO THE RULES APPLY ALSO TO ACTIVE SUBSTANCES CONTAINED IN AN IMPORTED FINISHED MEDICINAL PRODUCT?

10A: IS WRITTEN CONFIRMATION ALSO REQUIRED FOR A STARTING MATERIAL OR AN INTERMEDIATE USED FOR THE PRODUCTION OF AN ACTIVE SUBSTANCE, FOR EXAMPLE BY WAY OF PURIFICATION OR FURTHER SYNTHESIS?

11. IS THE WRITTEN CONFIRMATION ALSO REQUIRED FOR IMPORTED ACTIVE SUBSTANCES WHICH HAVE ALREADY BEEN MIXED WITH EXCIPIENTS, WITHOUT YET BEING THE FINISHED MEDICINAL PRODUCT?

11A. IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THE FINISHED DOSAGE FORM MANUFACTURED IN THE EU IS DESTINED FOR EXPORTATION ONLY?

＜問題＞

12. WHO CHECKS THAT THE IMPORTED ACTIVE SUBSTANCE IS ACCOMPANIED BY THE WRITTEN CONFIRMATION?

13. HOW CAN I CHECK IF THE WRITTEN CONFIRMATION IS AUTHENTIC?

14. IS THE WRITTEN CONFIRMATION SENT TO AN EU REGULATORY AGENCY?

15. DOES THE WRITTEN CONFIRMATION HAVE TO BE SUBMITTED WITH A REQUEST FOR AUTHORISATION OF A MARKETING AUTHORISATION OF A MEDICINAL PRODUCT?

16. IS THE WRITTEN CONFIRMATION TO BE ISSUED FOR EACH BATCH/CONSIGNMENT'?

17. DOES EACH IMPORTED CONSIGNMENT HAVE TO BE ACCOMPANIED BY THE WRITTEN CONFIRMATION?

＜問題＞

18. IS IT ACCEPTABLE THAT THE WRITTEN CONFIRMATION ACCOMPANYING THE IMPORTED CONSIGNMENT OF THE ACTIVE SUBSTANCE IS A COPY?

18A: REGARDING THE WRITTEN CONFIRMATION OF 'EQUIVALENT' STANDARDS OF GOOD MANUFACTURING PRACTICE, CAN THE ISSUING AUTHORITY OF THE NON-EU COUNTRY BASE ITSELF ON INSPECTION RESULTS FROM EU AUTHORITIES OR OTHER AUTHORITIES APPLYING EQUIVALENT STANDARDS FOR GOOD MANUFACTURING PRACTICE, SUCH AS US FDA?

18B: REGARDING THE WRITTEN CONFIRMATION OF 'EQUIVALENT' STANDARDS OF GOOD MANUFACTURING PRACTICE, CAN THE ISSUING AUTHORITY OF THE NON-EU COUNTRY BASE ITSELF ON INSPECTIONS CONDUCTED IN THE PAST?

＜問題＞

19. WHAT IS THE VALIDITY PERIOD OF THE WRITTEN CONFIRMATION?

19A. THE WRITTEN CONFIRMATION REFERS TO 'UNANNOUNCED INSPECTIONS'. DOES THIS MEAN THAT AN UNANNOUNCED INSPECTION HAS TO HAVE BEEN CONDUCTED?

20. IF ACTIVE SUBSTANCES ARE MANUFACTURED IN A NON-EU COUNTRY 'A', BUT IMPORTED IN THE EU VIA THE NON-EU COUNTRY 'B', WHO HAS TO ISSUE THE WRITTEN CONFIRMATION?

21. THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'CONFIRMATION NUMBER'. DOES THIS NUMBER HAVE TO BE A SEQUENTIAL NUMBER PER COUNTRY?

22.THE TEMPLATE FOR THE WRITTEN CONFIRMATION REFERS TO A 'RESPONSIBLE PERSON' IN THE ISSUING AUTHORITY. DOES THIS RESPONSIBLE PERSON HAVE TO HAVE A SPECIFIC QUALIFICATION?

＜問題＞

23. ACCORDING TO THE TEMPLATE FOR THE WRITTEN CONFIRMATION, INFORMATION OF FINDINGS RELATING TO NON-COMPLIANCE ARE SUPPLIED TO THE EU. TO WHOM THIS INFORMATION SHOULD BE SENT TO?

24. IS THE WRITTEN CONFIRMATION ALSO REQUIRED WHERE THERE IS A 'MUTUAL RECOGNITION AGREEMENT' BETWEEN A NON-EU COUNTRY AND THE EU?

25. IF A MANUFACTURING PLANT IS LOCATED IN A NON-EU COUNTRY 'A', CAN THE WRITTEN CONFIRMATION BE ISSUED BY AN AUTHORITY IN ANOTHER NON-EU COUNTRY (NON-EU COUNTRY 'B')?

26. ARE THERE EXCEPTIONS FROM THE REQUIREMENT OF A WRITTEN CONFIRMATION?

＜問題＞

27. WHERE CAN I FIND THE LIST OF NON-EU COUNTRIES TO WHICH THE REQUIREMENT OF A WRITTEN CONFIRMATION DOES NOT APPLY?

28. HOW MANY NON-EU COUNTRIES HAVE SO FAR REQUESTED TO BE LISTED?

29. WHEN IS THE LIST GOING TO BE PUBLISHED BY THE COMMISSION?

29A: HOW DOES A NON-EU COUNTRY REQUEST TO BE LISTED?

30. DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES (EDQM) OF THE COUNCIL OF EUROPE?

＜問題＞

31. DO I NEED A WRITTEN CONFIRMATION, EVEN THOUGH MY MANUFACTURING SITE HAS RECENTLY BEEN INSPECTED BY AN EU MEMBER STATE?

32. I WOULD LIKE TO BE INSPECTED BY AN EU MEMBER STATE. WHERE DO I 'APPLY' FOR SUCH AN INSPECTION?

33. WHAT HAPPENS WHEN AN ACTIVE SUBSTANCE MANUFACTURING SITE COVERED BY A WRITTEN CONFIRMATION IS FOUND GMP NON-COMPLIANT FOLLOWING AN INSPECTION BY AN EU MEMBER STATE?

34. WHERE CAN I FIND A LIST OF ACTIVE SUBSTANCE MANUFACTURING SITES THAT RECEIVED STATEMENTS OF GMP NON-COMPLIANCE?

35. CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED?

＜問題＞

7. IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS FOR MANUFACTURING OF ACTIVE SUBSTANCES ARE THE GOOD MANUFACTURING PRACTICES FOR ACTIVE SUBSTANCES OF THE WORLD HEALTH ORGANISATION (WHO) – FORTY-FOURTH TECHNICAL REPORT, NO. 957, 2010, ANNEX 2. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?

8. IN MY NON-EU COUNTRY, THE APPLICABLE STANDARDS ARE ICH Q7. ARE THESE STANDARDS EQUIVALENT TO THOSE IN THE EU, AS REQUIRED ACCORDING TO EU LEGISLATION?

＜答案＞（7&8）：**Yes.**

＜問題＞

26. ARE THERE EXCEPTIONS FROM THE REQUIREMENT OF A WRITTEN CONFIRMATION?

27. WHERE CAN I FIND THE LIST OF NON-EU COUNTRIES TO WHICH THE REQUIREMENT OF A WRITTEN CONFIRMATION DOES NOT APPLY?

28. HOW MANY NON-EU COUNTRIES HAVE SO FAR REQUESTED TO BE LISTED?

＜答案＞

26: The Commission publishes a list of countries which, following their request, have been assessed and are considered as having equivalent rules for good manufacturing practices to those in the EU. Active substances manufactured in these countries do not require a written confirmation.

27: The list is published in the Official Journal of the European Union and also reproduced here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

28: A list of non-EU countries which have so far requested to be listed is available here: http://ec.europa.eu/health/human-use/quality/index_en.htm.

Equivalence assessment

Status of current and past applications

Below is a list of third countries which have so far requested to be listed, as well as the status of the request:

Country	Date of request	Status, Date of publication in the Official Journal of the European Union
Switzerland	4 April 2012	Adopted, Commission implementing Decision (OJ L 325, 23.11.2012)
Israel	9 May 2012 3 september 2014	Adopted Commission implementing Decision (313 KB) (OJ L 171/23, 2.7.2015)
Australia	18 September 2012	Adopted, Commission implementing Decision (OJ L 113, 25.4.2013)
Singapore	17 September 2012	No listing for the moment (the relevant Singapore legislation provides for a non-mandatory GMP certification scheme). Contacts ongoing. In the meantime, Singapore issues written confirmation.

Equivalence assessment＜續＞

Status of current and past applications
Below is a list of third countries which have so far requested to be listed, as well as the status of the request:

Country	Date of request	Status, Date of publication in the Official Journal of the European Union
Brazil	4 October 2012	Adopted, Commission implementing Decision (313 KB) (OJ L 171/23, 2.7.2015)
Japan	6 December 2012	Adopted, Commission implementing Decision (OJ L 152/52, 5.6.2013)
United States	17 January 2013	Adopted, Commission Implementing Decision (OJ L 169/71, 21.06.2013)
New Zealand	26 June 2013	Assessment on hold pending clarification of the scope of the existing MRA
South Korea	22 January 2015	Equivalence assessment ongoing

＜問題＞

33. WHAT HAPPENS WHEN AN ACTIVE SUBSTANCE MANUFACTURING SITE COVERED BY A WRITTEN CONFIRMATION IS FOUND GMP NON-COMPLIANT FOLLOWING AN INSPECTION BY AN EU MEMBER STATE?

34. WHERE CAN I FIND A LIST OF ACTIVE SUBSTANCE MANUFACTURING SITES THAT RECEIVED STATEMENTS OF GMP NON-COMPLIANCE?

＜答案＞

33: A statement of GMP non-compliance issued by a EU Member State for a specific site and API supersedes the corresponding written confirmation until the noncompliance is resolved.

34:Statements of GMP non-compliance are stored in the EudraGMDP database (http://eudragmdp.eudra.org/inspections/displayWelcome.do) and publicly available.

＜問題＞

35. CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED?

＜答案＞

Article 46(b)(2)(b) sets out that active substances can only be imported if manufactured in accordance with EU GMP or equivalent, and accompanied by a written confirmation from the competent authority of the exporting third country certifying, inter alia, that

(1) the GMP standards applicable to the manufacturing plant are equivalent to those of the EU, and

(2) the supervision of the plant compliance with GMP ensures a protection of public health equivalent to that of the EU.

＜問題＞

35. CAN AN API BATCH MANUFACTURED DURING THE PERIOD OF VALIDITY OF A WRITTEN CONFIRMATION BE IMPORTED INTO THE EU ONCE THE WRITTEN CONFIRMATION IS EXPIRED? ＜續＞

＜答案＞

It is legitimate to consider that the guarantees of equivalence provided by the written confirmation apply to any API batch in the scope of the written confirmation which was released for sale within the period of validity of the written confirmation, even if not exported in that time period.

Against this background, it can therefore be considered that the importation into the EU of an API accompanied by an expired WC is acceptable provided that the paperwork accompanying the consignment (1) unequivocally proves that the whole consignment has been manufactured and released for sale by the quality unit before the expiry date of the written confirmation; and (2) provides a solid justification of why a valid written confirmation is not available.

5. FDA
Questions and Answers on Current Good Manufacturing Practices for Drugs 2015

SpecificTopics:

- General Provisions
- Organization and Personnel
- Buildings and Facilities
- Equipment
- Control of Components and Drug Product Containers and Closures
- Production and Process Controls
- Packaging and Labeling Control
- Holding and Distribution
- Laboratory Controls
- Records and Reports
- Returned and Salvaged Drug Products

＜附註＞

FDA是於2002年初始發佈本文件並視需要增補，其目的是：

- to help FDA be more transparent with CGMP policy
- to clarify statements of existing requirements or policy
- intend to use this format to provide timely answers to questions about the meaning and application of CGMPs for human, animal, and biological drugs, and to share these widely

➢以下資訊係僅擷取其2015年以後新增部分

Questions and Answers on Current Good Manufacturing Practices—Equipment

5. What are the cleaning validation requirements for potent compounds (e.g., compounds that are cytotoxic, mutagenic, or have high pharmacologic activity), and is dedicated equipment required?
6. How do I perform cleaning validation, including for homeopathic drug products?
7. Does equipment need to be clean enough to meet limits based on the most sensitive possible methods of residue detection or quantification?
8. Do firms need to quantify the total amount of residue remaining on equipment surfaces after manufacturing a product (before cleaning) to support cleaning validation studies?
9. Should laboratory glassware be included in a firm's equipment cleaning validation program?

Questions and Answers on Current Good Manufacturing Practices—Equipment＜續＞

10. What is an acceptable level of detergent residue, and what is the basis for arriving at this level, if any?
11. If a procedure's ability to clean a piece of equipment made of a particular material, such as 316 stainless steel, is acceptable and validated, can that "material-specific" cleaning procedure be applied to other pieces of equipment and compounds without extensive validation?
12. Is testing rinse solution enough to support residue determinations for cleaning validation?
13. Does FDA prefer one type of material over another (e.g., polyvinylidene difluoride over stainless steel) for construction of recirculating loops in water for injection (WFI) systems?

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Control of Components and Drug Product Containers and Closures

14. Must each batch of a United States Pharmacopeia (USP)-grade API be tested using the analytical procedures specified in the USP monograph?

Questions and Answers on Current Good Manufacturing Practices—Production and Process Controls

19. For a nonsterile compendial drug product that includes an antimicrobial preservative in its formulation, may I release and market lots of this drug product with initial out-of-specification total aerobic plate counts if these lots test within specification 2 weeks later?

Questions and Answers on Current Good Manufacturing Practices—Production and Process Controls＜續＞

20. Do pharmaceutical manufacturers need to have written procedures for preventing growth of objectionable microorganisms in drug products not required to be sterile? What does objectionable mean anyway?
21. For drug products formulated with preservatives to inhibit microbial growth, is it necessary to test for preservatives as part of batch release and stability testing?

Questions and Answers on Current Good Manufacturing Practices—Production and Process Controls

8. How do I contact CDER with questions about PAT?

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Laboratory Controls

10. Is it acceptable to release non-penicillin finished drug products to market if the products may have been exposed to penicillin, as long as the non-penicillin products are tested and no penicillin residue is found?

11. Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility?

12. Is there an acceptable level of penicillin residue in non-penicillin drug products?

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Laboratory Controls＜續＞

13. For injectable drugs in multiple-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date?

14. How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in finished drug products?

Questions and Answers on Current Good Manufacturing Practices—Equipment

＜問題＞

5. What are the cleaning validation requirements for potent compounds (e.g., compounds that are cytotoxic, mutagenic, or have high pharmacologic activity), and is dedicated equipment required?

＜答案＞

Separation or dedication of equipment and facilities for the manufacture of potent compounds is not specifically required by CGMP regulations. However, manufacturers should identify drugs with such risks and define the controls necessary to eliminate risk of product cross-contamination in nondedicated equipment and facilities. Such controls include proper cleaning, cleaning validation, and other contaminant controls. Firms must validate that cleaning procedures are adequate to ensure that cross-contamination does not occur. CGMP regulations establish requirements to guide development and execution of cleaning validation plans.
In designing a facility, firms should carefully evaluate manufacturing processes to determine the best procedural controls and floor plan—optimizing the flow of materials, equipment, and people—to help prevent product contamination.

Questions and Answers on Current Good Manufacturing Practices—Equipment

＜問題＞

7. Does equipment need to be clean enough to meet limits based on the most sensitive possible methods of residue detection or quantification?

＜答案＞

No. CGMPs require that equipment be cleaned to prevent contamination that "would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 21 CFR 211.67). The preamble to the CGMP regulations (see 43 FR 45014) indicates that this phrase was added because absolute cleanliness for multiuse equipment is neither valuable nor feasible in many circumstances. The degree of cleanliness needed, therefore, cannot depend on the method of detection because improvements in method sensitivity would necessitate ever-lower limits and ever-increasing wash cycles. Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues. Contamination that is reasonably avoidable and removable is never considered acceptable.

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Control of Components and Drug Product Containers and Closures

＜問題＞

14. Must each batch of a United States Pharmacopeia (USP)-grade API be tested using the analytical procedures specified in the USP monograph?

＜答案＞

No; however, in the event of a dispute, the compendial method is considered conclusive (see USP reference, below). Section 201(g) of the FD&C Act includes "articles intended for use as a component" of a finished drug product, including APIs (or drug substances), under its definition of a drug, and section 501(b) requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards. Although each batch of a compendial article must conform to the monograph specifications/acceptance criteria, the analytical procedures used to show conformance may differ from official USP methods if the alternative methods are fully validated, suitable for use, and give equivalent or better results than the official USP method.
All APIs must also be manufactured in compliance with CGMP as stated in section 501(a)(2)(B) of the FD&C Act.

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance —Laboratory Controls

＜問題＞

11. Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility?

＜答案＞

Yes; however, decontamination can be extremely difficult. The decontamination process must include scientifically sound studies demonstrating the efficacy of the decontamination agents, extensive and statistically appropriate sampling throughout the areas before and after decontamination to verify cleanliness, and appropriate testing of such samples with a validated analytical method having an appropriate limit of detection. The CGMP regulations in 21 CFR 211.176 require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and cannot be marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present if decontamination has not been conducted effectively. Although CGMP regulations do not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues can make the process daunting (see also FDA Guide to Inspections, referenced below).

6. FDA

Guidance for Industry

ANDAs: Stability Testing of Drug Substances and Products

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2014
Generics

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＜問題＞A. General

Q1: What is the scope of and implementation date for the FDA stability guidance?

Q2: How will this guidance affect the President's Emergency Plan for AIDS Relief (PEPFAR) and positron emission tomography (PET) ANDAs?

Q3(i): Can an ANDA be submitted with 6 months of accelerated stability and 6 months of long-term stability data?

Q3(ii): When do intermediate stability studies need to be initiated in the event of failure at accelerated condition?

Q3(iii): If one among the three batches in accelerated conditions shows a significant change, what should be done?

＜問題＞A. General

Q4: Can stability bracketing and/or matrixing be used to determine the packaging configurations to be placed on stability for an original ANDA without prior approval from the Office of Generic Drugs (OGD)?

Q5(i): If an application that qualifies for the Generic Drug User Fee Act (GDUFA) 10-month review is filed with 6 months of accelerated and 6 months of long-term data, and there are no blocking patents or exclusivities, will 24 months of shelf life be granted?

Q5(ii): During the review cycle, will the application need to be updated with 12 months of long-term data?

＜問題＞A. General

Q6: Can only two lots of finished product at pilot scale batch size ever be considered sufficient to support the stability of an ANDA for simple dosage forms?

Q7: How is the proposed shelf life supposed to be calculated? Will 6 months of accelerated data equal 24 months at long-term? ·

Q8: Will the recommendation for 6 months accelerated data be met by providing 24 weeks of data as 12 weeks is typically accepted as equivalent to 3 months?

Q9: When a patent is due to shortly expire and there are no approved ANDAs, can we file with 3 months stability data with a commitment to supply 6 months data when available?

Q10: How long do the three pilot scale batches, submitted as a part of an ANDA, need to be stored before destruction?

＜問題＞與＜答案＞A. General

Q3(i): Can an ANDA be submitted with 6 months of accelerated stability and 6 months of long-term stability data?

Q3(ii): When do intermediate stability studies need to be initiated in the event of failure at accelerated condition?

Q3(iii): If one among the three batches in accelerated conditions shows a significant change, what should be done?

A3(i): Yes. An ANDA applicant should submit 6 months of accelerated stability data and 6 months of long-term stability data at the time of submission. However, if 6 months of accelerated data show a significant change or failure of any attribute, the applicant should also submit 6 months of intermediate data at the time of submission.

A3(ii): An ANDA applicant should start accelerated, intermediate, and long-term stability studies at the same time so the data are available at the time of submission if the accelerated stability study fails.

A3(iii): If accelerated data show a significant change or failure of any attribute in one or more batches, an applicant should submit intermediate data for all three batches. In addition, the submission should contain a failure analysis (i.e., discussion concerning the observed failure(s)).

＜問題＞B. Drug Master File

Q1: Please clarify the effect of the FDA stability guidance on Drug Master File (DMF) holders.

Q1(i): How many months of long-term and accelerated data are required when a "Completeness Assessment" is performed on the DMF? Also, what should the DMF stability section contain for a Completeness Assessment?

Q1(ii): Are stability data from three current good manufacturing practice (CGMP) batches required to be filed in the DMF to support the API retest date? Also, how many months of long-term and accelerated data are required for pilot scale batches?

Q2: Will submissions to DMFs be accepted based on stability data from production scale batches?

Q3: Should executed batch records for the three batches be included in the DMF submission?

B. Drug Master File

＜問題＞

Q1(ii) :Are stability data from three current good manufacturing practice (CGMP) batches required to be filed in the DMF to support the API retest date? Also, how many months of long-term and accelerated data are required for pilot scale batches?

＜答案＞

A1(ii): Yes. Per ICH Q1A(R2) data from formal stability studies should be provided on at least three primary batches 9 and the batches should be manufactured to a minimum of pilot scale 10 for the drug substance to be filed in the DMF. These batches should be made under CGMPs. The FDA stability guidance recommends 6 months of accelerated data and 6 months of long-term data for the pilot scale batches to be submitted for a full scientific review of the DMF. Additional long-term data for all three batches, as the data becomes available through the proposed retest period, should be submitted as an amendment.

＜問題＞

C. Drug Product Manufacturing and Packaging

Q1: Can the split bulk solution filled into different fill volumes be considered discrete batches?

Q2: Can you clarify the packaging recommendations for the submission batches for blow-fill-seal containers?

Q3: Should all three batches be stored in final proposed packaging?

Q4: What is the Agency's position on using different lots of APIs and/or packaging materials? How many API lots should be used in the manufacture of finished product lots used to support the ANDA?

Q5: Should the small scale batches be packaged with commercial equipment? Also, is it acceptable to package using research equipment or by hand?

Q6: What will the recommendation for secondary packaging be?

＜問題＞

C. Drug Product Manufacturing and Packaging

Q7: What are the recommendations for stability testing data of modified release dosage forms?

Q8: What are the recommendations for the submission of oral solutions, ophthalmic solutions, oral and ophthalmic suspensions, transdermal patches, ointments, creams, granules for reconstitution, and parenterals?

Q9: Are 6 months of stability data required on all three batches, or would one batch at 6 months and two lots at 3 months be acceptable?

Q10: Should the executed batch records for the three batches be included in the ANDA submission?

Q11: Does all relevant CMC batch information for the three stability batches need to be included in the application?

＜問題＞

C. Drug Product Manufacturing and Packaging

Q12: If you are an applicant submitting an ANDA with two API sources, are you required to perform stability on three batches of drug product for each API source?

Q13: What is meant by "small" scale? "Small" is not a defined word in ICH guidance. What are the packaging expectations from the small batch, as well as from the two pilot scale batches? Traditionally, ANDAs are submitted with 100,000 units for solid oral dosage forms. Is this still applicable?

Q14: Is it acceptable to use a technical grade of the drug substance for the small scale batches or one of the two pilot scale batches of finished drug product?

＜問題＞

C. Drug Product Manufacturing and Packaging

Q15: Do the small scale batches need to be manufactured in accordance with all CGMP regulations, or is it acceptable to manufacture the small scale batches in a research setting?

Q16: Should the small scale batches meet the same finished product specification as the pilot scale batches?

Q17: For sterile products, is it acceptable to manufacture the small scale batches in a nonsterile facility and allow variance from sterility and particulate criteria?

Q18: Should small scale batches be produced at the proposed commercial site?

Q19(i): In cases where an intermediate bulk material is identical between the various strengths (dose proportional blends, bulk solutions, etc.), is it sufficient to perform stability on one lot of each strength, when each strength is produced from a separate intermediate bulk?

＜問題＞

C. Drug Product Manufacturing and Packaging

Q19(ii): Are differences in the capsule shell (i.e., imprint, color, size, etc.), allowed in cases where a multi-strength capsule product is dose-proportional across all strengths (based on common bead blend)?

Q20: What are the criteria for an exception to the recommendations regarding minimum size for pilot scale for ANDA submission batches?
What justification would be needed if we wanted to deviate from these guidance recommendations?

Q21: Are scale-up and postapproval changes (SUPAC) level one and two variations and changes permitted among the three ANDA submission batches for components and composition?

＜問題＞

C. Drug Product Manufacturing and Packaging

Q22: Can FDA provide specific examples of cases where statistical analysis is required and the type of statistical analysis needed?

Q23: How many batches of drug product should be tested for split-portions of scored tablets?

Q24: For drug products that include placebo tablets, how many batches (of placebo tablets) are required for submission? Is 6 months of stability data on the placebo tablets needed if the ANDA is submitted after the June 2014 deadline?

C. Drug Product Manufacturing and Packaging

＜問題＞

Q13: What is meant by "small" scale? "Small" is not a defined word in ICH guidance. What are the packaging expectations from the small batch, as well as from the two pilot scale batches? Traditionally, ANDAs are submitted with 100,000 units for solid oral dosage forms. Is this still applicable?

＜答案＞

A13: The interpretation of what constitutes a small scale batch for the purpose of filing ANDAs is further elaborated below for various dosage forms and their packaging recommendations. Unless specifically noted below, one primary batch should be fully packaged.

Q13＜問題＞與＜答案＞（續）

Oral dosage forms

(a) Tablets/Capsules (e.g., immediate release, extended release, chewable, orally disintegrating and delayed release tablets or capsules):

Two of the three batches should be of at least 10 percent of the proposed production batch or 100,000 finished dosage units, whichever is greater (i.e., pilot scale batches). The third batch can be smaller than the 10 percent of the proposed production batch, but should not be less than 25 percent of the pilot scale batch. We recommend stability data be generated for the three ANDA submission batches in the proposed marketing container. A minimum of 100,000 units in all proposed presentations is recommended. Representative samples from all three batches must be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1 -5) and 211.166(b) .

Q13＜問題＞與＜答案＞（續）

Oral dosage forms

(b) Powders/Solutions/Suspensions:

Two of the three batches should be at least 10 percent of the proposed maximum size commercial batch. The third batch can be smaller than 10 percent of the proposed commercial batch, but should not be less than 25 percent of the pilot scale batch. To capture variability introduced by packaging, the product from all the batches should be used in the packaging process. We recommend packaging representative samples from all three batches of a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b)

Q13＜問題＞與＜答案＞（續）

Parenterals

Solutions/Powders for Solutions (lyophilized cakes)/ Suspensions/ Sterile Topicals (Ophthalmic and Otic drug products):

Two of the three batches should be at least (a) 10 percent of the proposed maximum size commercial batch (i.e., pilot scale size), (b) 50 L (per batch if the fill volume configurations per vial is larger than 2.0 mL), or (c) 30 L (per batch if the fill volume size is up to 2.0 mL) whichever is larger including packaging*. When multiple fill volume sizes are proposed by the applicant (e.g., 1 mL, 2 mL, and 3 mL), then 50 L per batch size is recommended. The third batch can be smaller than 10 percent of the proposed commercial batch, but should not be less than 25 percent of the pilot scale batch (with packaging). To capture variability introduced by packaging*, the product from each of multiple fill volume batches should be used in the packaging process. We recommend manufacturing all the batches to meet sterility requirements. Packaging requirements are also discussed in 21 CFR 211.166(a) (1 -5) and 211.166 (b).

***Amount packaged = 50 L or 30 L –(minus) filling/flushing loss**

Q13＜問題＞與＜答案＞（續）

Transdermal Patches

- Two of the three batch sizes for each strength should be at least 10 percent of the proposed commercial production batch (with packaging) or 25,000 units (for each strength), whichever is greater. The third batch can be smaller than 10 percent of the proposed commercial batch (with packaging), but should not be less than 60 percent of the pilot scale batch (with packaging).
- For transdermal matrix products, where different strengths are identified by the transdermal patch size (surface area), to comply with the three batch size recommendation, we recommend providing data on patches manufactured using three distinct matrix laminates at the time of submission (each laminate can be cut to support multiple strengths in the application, where applicable).
- We recommend you contact the appropriate OGD review division if you are manufacturing transdermal patches using other technologies (e.g., reservoir)
- You should include a representative sample from all three batches using different components of backing, adhesives, release liner, and other critical excipients used in packaging a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

Q13＜問題＞與＜答案＞（續）

Topicals

(a) Creams/Lotions/Gels:

For nonsterile semi-solid dosage forms, the two pilot scale batches should be at least 100 Kg or 10 percent of the production batch, whichever is larger, packaged*. The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 40 percent of the pilot scale batch, packaged*. Packaging requirements are also discussed in 21 CFR 211.166(a) (1 -5) and 211.166 (b).

***Amount packaged = 100 Kg or Larger –(minus) filling/flushing loss.**

(b) Inhalation Solutions/Nasal Sprays (nasal nonmetered dose atomizer):

Please refer to the following guidances for industry for information: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products –Chemistry, Manufacturing, and Controls Documentation*, and *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.
Please contact OGD to discuss other dosage forms and/or routes of administration not covered in this document.

＜問題＞

D. Amendments to Pending ANDA Application

Q1: What are the recommendations for amendments and responses filed to pending ANDAs after issuance of the final FDA stability guidance?

＜問題＞

E. Stability Studies

Q1: What will be the expected testing time points on accelerated conditions?

Q2: Can the Agency clarify expectations for the storage positions for products placed into the stability program?

Q3: When and how are reconstitution/dilution studies performed?

Q4: What types of containers are classified as semipermeable containers, and can the Agency clarify the stability expectations for the drug products in semipermeable containers?

Q5: Can the Agency clarify expectations around the number of batches to support tests such as preservative effectiveness and extractable/ leachable testing?

Q6: When are in-use stability studies needed?

Q7: Are there changes to postapproval protocols and commitments when ICH stability guidances are implemented because of scale or type of batches submitted?

E. Stability Studies

＜問題＞與＜答案＞

Q1: What will be the expected testing time points on accelerated conditions?

Q2: Can the Agency clarify expectations for the storage positions for products placed into the stability program?

A1: The applicant should test at 0 (initial release), 3, and 6 months; for additional time points on accelerated conditions, please follow ICH Q1A(R2) recommendations for all ANDAs.

A2: For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position. For routine stability studies, the applicant should pick the worst case orientation for the study.

＜附注＞ **Primary batch**

ICH Q1A(R2)

A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

7. ICH

Q7 Guideline
Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Questions and Answers
Current version
dated 10 June 2015

ICHQ7 Implementation Working Group

The International Council for Harmonisation (ICH)

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7.3 What is expected in terms of evaluation of suppliers of materials?
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11. 2 When is it acceptable for an API manufacturer to extend an API retest date [ICH Q7, Section 11.6]?
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12.1 Is the lifecycle approach to process validation acceptable for APIs under ICH Q7?
12.2 Can the range of a process parameter be expanded based only on a process deviation(s)?
12.3 Would additional process validation studies be needed to support a change in the source of an API starting material?

12.4 Is a retrospective approach to validation still acceptable?
13.1 Who is responsible for notifying the drug product manufacturer about relevant changes in API manufacturing?
14.1 Should rejected materials be stored under physical and secure segregation?
14.2 Does the definition of expiry date in ICH Q7 preclude the rework or reprocess of an expired API?
14.3 Is validation expected for the recovery of material from mother liquor?
15.1 Can quality defects of released APIs that are identified by another entity belonging to the same company be handled outside of the API manufacturer's complaint procedure?
15.2 Must a quality related return, at the request of the API manufacturing site, from another site within the same company be recorded as a 'recall'?
16.1 Does ICH Q7 preclude a contract manufacturer's independent quality unit from performing the main responsibilities as described in [ICH Q7, Section 2.22]?

16.2 Which outsourced activities are covered by ICH Q7?
16.3 What is meant by 'where subcontracting is allowed' [ICH Q7, Section 16.14]?
17.1 What does ICH Q7 mean by 'Agents, brokers, traders, distributors, repackers, or relabellers'?
17.2 Could a distributor of an API engage a contract manufacturer for production Steps?
17.3 Is it acceptable to replace the original label, which contains the information of the original manufacturer?
17.4 Who is considered to be the original manufacturer of the API for purposes of the Certificate of Analysis (CoA)?
18.1 Does ICH Q7 expect validation for viral removal/viral inactivation steps for biological/biotechnological products?
18.2 Do [ICH Q7, Sections 18.14, 18.2] apply to classical fermentation and biotechnology?
19.1 Is it permitted to use the same equipment to manufacture materials to be used in pre-clinical and clinical trials?
20. Are the terms 'deviation' and 'nonconformance' synonyms?

4. BUILDINGS AND FACILITIES－CONTAINMENT

＜問題＞

4.2 To what extent can quality risk management be used in establishing appropriate containment measures to prevent cross-contamination?（June 2015）

＜答案＞

The principles of quality risk management [ICH Q9, Annex II.4] should be applied to the design of buildings, facilities and controls for the purpose of containment, taking into consideration the pharmacological/toxicological/chemical/biological properties of the raw material, intermediate and/or API to be handled or manufactured. Appropriate containment measures and controls [ICH Q7, Section 4.42] include but are not limited to the following:

- Technical controls (e.g., dedicated production areas, closed/dedicated Heating Ventilation and Air Conditioning (HVAC) system, closed manufacturing systems, use of disposable technologies, design of facility and equipment for containment and ease of cleaning); and
- Procedural (organisational) controls (e.g., cleaning, personnel flow, environmental monitoring and training).

Monitoring systems are important to check the effectiveness of the containment controls.

11. LABORATORY CONTROLS

＜問題＞

11. 2 When is it acceptable for an API manufacturer to extend an API retest date [ICH Q, Section 11.6]?（June 2015）

＜答案＞

The purpose of a retest date is to ensure that the API is still suitable for use. The API manufacturer can extend the retest date of a specific batch based on good science and long-term stability results for that API and testing of the specific batch that has been stored according to the label conditions. In some regions, regulatory authority approval of the retest date extension for the batch may be required. If an API manufacturer wants to change (i.e., extend) the retest date for future batches of an API, then it should conduct stability testing sufficient to support the change, and include the new retest date and supporting data in a regulatory filing, as determined by regional requirements.

14. REJECTION AND REUSE OF MATERIALS

＜問題＞

14.2 Does the definition of expiry date in ICH Q7 preclude the rework or reprocess of an expired API?（June 2015）

＜答案＞

According to the definition, material should not be used after the expiry date. The original intent of this definition in ICH Q7 was that expired API should not be used in drug product formulation. It may be acceptable to reprocess [ICH Q7, Section 14.2] or rework [ICH Q7, Section 14.3] the expired API where the API manufacturer has all related historical GMP documentation and additional stability data on the reworked or reprocessed API. There may be registration/filing considerations that are beyond the scope of ICH Q7 in addition to the GMP considerations.

8.USP

Water for Pharmaceutical Purposes ＜1231＞

【2S (USP39)】

Recommended sanitising temperatures	
USP＜1231＞Water for Pharmaceutical Purposes	65-80˚C
ISPE Guide Volume 4 “Water and Steam”	80 ± 3˚C
FDA Guide to inspections on high purity water systems	65-80˚C
WHO Technical Report 929	70-80˚C

- Temperatures of 65˚–80˚C are most commonly used for thermal sanitization.
- Continuously recirculating water of at least 65˚C at the coldest location in the distribution system has also been used effectively in stainless steel distribution systems when attention is paid to uniformity and distribution of such self-sanitizing temperatures.
- The use of thermal methods at temperatures significantly above 80˚ is contraindicated because it does not add to microbial control of the system or reduction of biofilm.
- Some methods (e.g., steam sanitizing, hot water circulation at temperatures ≥100˚) can be less effective or even destructive because of the need to eliminate condensate or manipulate system components, stress materials of construction, deform filters, and its adverse impact on instrumentation.

USP＜1231＞Water for Pharmaceutical Purposes【2S (USP39)】

Example Culture Methods

Culture Methods	Drinking Water	Purified Water	Water for Injection
1. Pour Plate Method 2. Membrane Filtration Method [a]	1 or 2	1 or 2	2
Suggested Sample Volume [b] : 1. 1.0 mL for pour plate 2. 100 mL for membrane filtration 3. 200 mL for membrane filtration	1	1 or 2	3
Growth Medium [c]	Plate Count Agar	Plate Count Agar	Plate Count Agar
Incubation Time [d]	48–72 h	48–72 h	48–72 h
Incubation Temperature [e]	30˚–35˚C	30˚–35˚C	30˚–35˚C

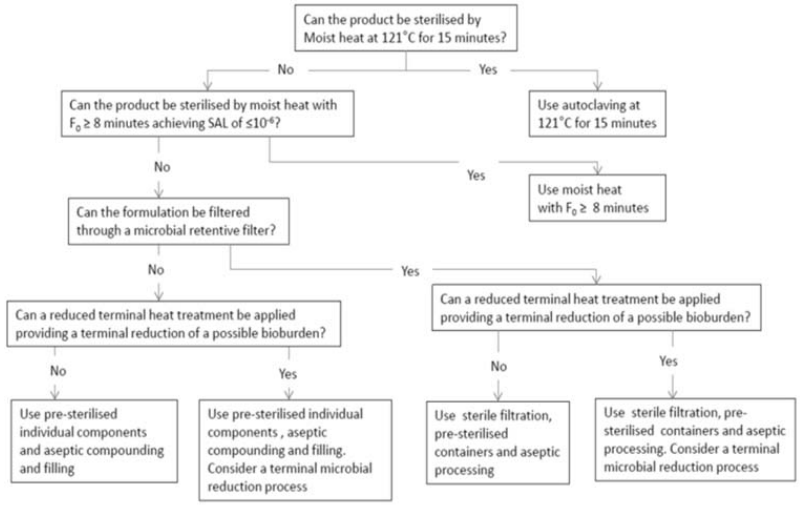
[a] A membrane filter with a rating of 0.45 µm is generally considered preferable to smaller porosity membranes.
[b] Sample size must be appropriate for the expected microbial count of the water in order to derive statistically valid colony counts.
[c] For optimum recovery, an alternative medium may be more appropriate (e.g., m-HPC, TSA/SCDA, R2A).
[d] For optimum recovery, alternative incubation times may be needed.
[e] For optimum recovery, alternative incubation temperatures may be needed.

9. EMA

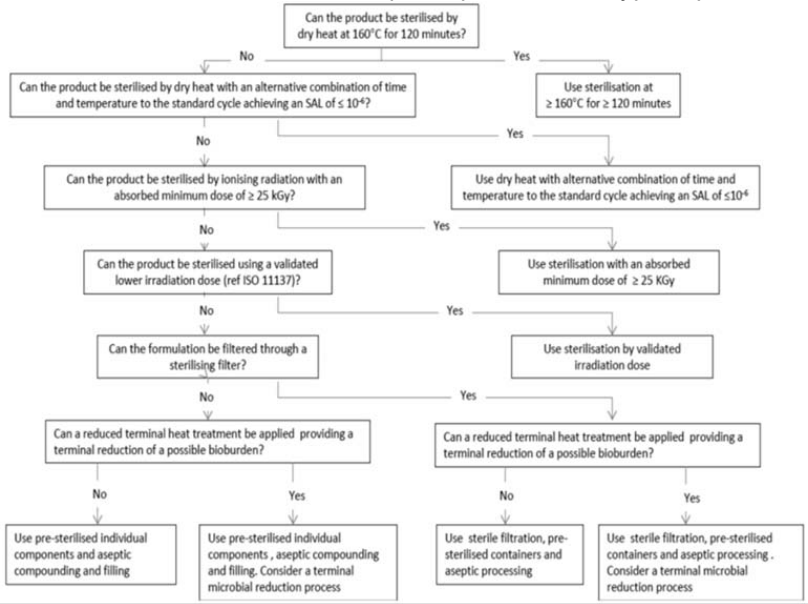
Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container ＜Draft＞

11 April 2016
EMA/CHMP/CVMP/QWP/BWP/850374/2015
Committee for Medicinal Products for Human use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)
Quality Working Party (QWP)
Biologics Working Party (BWP)

Decision tree for sterilisation choices for aqueous products



Decision tree for sterilisation choices for non-aqueous liquid, semi-solid or dry powder products



GMP Advisor

The GMP Questions & Answers Guide

Version 01 of April 2014

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GMP Advisor
About this document

- **Searching for concrete answers to GMP questions is a time-consuming activity.**
- **This document is intended to provide a single source of information.**
- **We have summarized GMP questions and answers from Regulators around the world.**
- **In addition to EMA, FDA, Health Canada, MHRA (UK), TGA (Australia) and ICH we have also used Q&As from ECA.**
- **The subject index contains some of the "GMP Key Words" and allows to find Q&As addressing the relevant topic.**
- **It is the intension to update this comprehensive collection and to also add new Q&As once they are available**

FDA Warning Letter
Beijing Taiyang（太洋）Pharmaceutical Industry Co Ltd
＜10/19/16＞

1. **Your firm delayed, denied, or limited an inspection, or refused to permit the FDA inspection.**
2. **Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.**
3. **Failure to ensure that all quality-related activities are recorded at the time they are performed.**
4. **Failure to ensure that all quality-related activities are recorded at the time they are performed.**

Data Integrity Remediation

FDA Warning Letter
Teva Pharmaceutical Works Private Limited Company ＜10/13/16＞

1. **Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. (21 CFR 211.192)**
2. **Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))**
3. **Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(iv))**
4. **Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. (21 CFR 211.160(b))**
5. **Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards. (21 CFR 211.194(a))**
6. **Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records. (21 CFR 211.68(b))**
7. **Your firm failed to follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch. (21 CFR 211.186(a))**

Data Integrity Remediation

FDA Warning Letter

- If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law.
- Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

FDA Warning Letters
SmithKline Beecham Limited（GSK House）
UNITED KINGDOM
＜6/30/16＞

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API)

1. **Failure to have appropriate procedures (or practices) in place to prevent cross-contamination from dedicated penicillin manufacturing area to non-dedicated areas.**
   - **A. Penicillin cross contamination**
   - **B. Penicillin detection method validation**
   - **C. Penicillin cleaning method validation**
1. **Failure to adequately investigate critical deviations and implement corrective and preventive actions.**
   - **A. Microbial contamination in (b)(4) water systems**
   - **B. (b)(4) API batch (b)(4) with out-of-specification bioburden**
   - **C. Foreign particles found in (b)(4) API (b)(4)**