Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Questions and Answers

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)

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ICH

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Contains Nonbinding Recommendations

TABLE OF CONTENTS

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Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION (Preface)

The ICH guidance *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess.

Since the ICH Q7 Guidance was finalized, experience with implementing the guidance worldwide has given rise to requests for clarification of uncertainties due to the interpretation of certain sections. This question and answer (Q&A) document is intended to respond to those requests.

The ICH Q7 document should be read in its entirety regardless of the nature of the manufacturing activities being conducted to fully understand the linkages between certain sections and successfully implement appropriate good manufacturing practices (GMPs) at all stages of the active pharmaceutical ingredients (API) supply chain, including distribution. A table is provided as an annex of this document showing the link between each Q&A and the relevant sections of ICH Q7 and other ICH Quality guidance.

ICH would like to acknowledge the work undertaken by the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S contributed to this document by selecting and reviewing relevant Q&As that had been collected from training sessions since the implementation of Q7

[1] This guidance was developed within the Q7 Implementation Working Group (IWG) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. The Q&As in this document have been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, June 2015. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and North America.

and transferred the output of these reviews to the ICH Q7 IWG for consideration and consolidation, as appropriate. Additional questions were developed based on responses from an ICH survey. PIC/S further contributed to the development of the document as an ICH Interested Party.

Please note that ICH Q7 should be applied in combination with the principles laid down for development and manufacturing in ICH Q11 (see definition of API starting material; see also ICH Q8(R2) Part II),[2] *Quality Risk Management* (ICH Q9), and *Pharmaceutical Quality Systems* (ICH Q10). GMP principles described in ICH Q7 should be applied regardless of which approach is taken in pharmaceutical development and manufacturing.

ICH Q7 also describes principles of GMPs to be applied in the manufacture of APIs for use in clinical trials (section XIX (19)) and for APIs manufactured by cell culture/fermentation (section XVIII (18)).[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. Scope (1)

1.1: Should GMP according to ICH Q7 be applied for manufacturing steps before the defined* API starting material*, i.e., steps not identified in grey in Table 1?

ICH Q7 does not apply to steps prior to the introduction of the API starting material. However, there is an expectation that an appropriate level of controls suitable for the production of the API starting material should be applied (ICH Q7, section I.C (1.3)).

Normally, the *API-starting material* is defined in the regulatory filing by the applicant and approved in the regulatory reviewing process. Additional guidance is provided to define and justify *API starting material* derived from various sources (ICH Q11, section V (5)); for master cell banks, see ICH Q5B, ICH Q5D.

1.2: Does ICH Q7 apply to manufacturing steps for the addition of substance(s) to an API (e.g., to stabilize the API)?

[2] The reference list at the end of this ICH Q7 Q&A guidance contains details of other ICH guidances cited.

[3] The Arabic numbers in parentheses reflect the organizational breakdown in the ICH Q7 document and this Q7 Q&A document endorsed by the ICH Steering Committee in November 2000 and June 2015, respectively.

When a mixture is classified in the regulatory filing as an API in a region or country in which it is used in a drug product, ICH Q7 should be applied to the manufacturing of the mixture (ICH Q7, section I.B (1.2), Glossary (20) — see Glossary for definition of *API*).

B. Quality Management (2)

2.1: What is meant by "quality unit(s) independent from production"?

The intent of the term *independent* is to prevent any conflict of interest and ensure unbiased decision-making regarding quality-related decisions in the organization structure. The person in the quality unit who is responsible for final decision-making (e.g., batch release decision) should not have responsibilities for production activities (ICH Q7, paragraph 2.13)[4].

2.2: Does ICH Q7 expect that the quality unit performs API release testing?

While the quality unit has responsibility for the release of the API, which includes oversight of the testing and results, ICH Q7 does not prescribe specifically who performs testing. The term *quality control* in the ICH Q7 Glossary (section 20) refers to the activities, not the organizational structure.

For examples of quality responsibility related to testing and release, refer to ICH Q7, paragraphs 2.13, 2.22, and 11.12. Appropriate laboratory controls should be followed (ICH Q7, paragraphs 11.10, 16.10) regardless of who performs the testing.

2.3: Can other departments outside of the quality unit be held responsible for releasing raw materials and intermediates?

Yes. The quality unit is responsible for establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials. This responsibility cannot be delegated (ICH Q7, paragraph 2.22(2)). The system established by the quality unit may allow other departments to release raw materials and intermediates (except intermediates that are for use outside the control of the manufacturer (ICH Q7, paragraph 2.22(1)) as long as oversight and the overall responsibility of this system remains with the quality unit.

2.4: Does ICH Q7 expect that sampling be performed by the quality unit?

No. ICH Q7 does not prescribe specifically who should perform the sampling (ICH Q7, paragraph 2.22). However, the quality unit has responsibility for reviewing and approving sampling plans (ICH Q7, paragraph 11.12) and procedures. Sampling should

[4] Arabic numbers preceded by the word "paragraph" reflect specific paragraphic numbers in ICH Q7.

be performed by adequately trained personnel (ICH Q7, paragraph 3.10) and be appropriately documented per ICH Q7, paragraph 6.52.

2.5: What should be the frequency of a product quality review?

A product quality review is generally expected annually. Review time frames can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. Even if no manufacturing has occurred in the review period, the quality review should be conducted per section ICH Q7, paragraph 2.50, and include stability, returns, complaints, and recalls.

For example, a product quality review may encompass more or less than 12 months depending upon product campaign duration (ICH Q7, paragraph 2.50; ICH Q10, section III.F (2.6)).

2.6: Should the product quality review of results include trend analysis?

Trend analysis is usually an important element in verifying the consistency of the process as part of the product quality review (ICH Q7, paragraphs 2.50, 2.51). Potential tools to use are described in ICH Q9, Annex I.9.

C. Personnel (3)

3.1: What is the intent of the statement in ICH Q7, paragraph 3.12 "training should be periodically assessed"?

In ICH Q7, paragraph 3.12, the statement "training should be periodically assessed" refers to a system to evaluate if personnel remain proficient and competent in their job tasks and responsibilities, whether more frequent, additional, or new training is needed, and if recurring training is up to date.

3.2: Does ICH Q7 expect the use of a consultant, and can a company delegate tasks and/or responsibility to a consultant?

ICH Q7 does not expect the use of a consultant. Consultants may perform delegated tasks and/or provide advice. However, the ultimate responsibility for API quality must not be delegated (ICH Q10, section III.G (2.7); ICH Q7, sections II.B (2.2), III.C (3.3)).[5]

D. Buildings and Facilities — Containment (4)

4.1: When are dedicated production areas expected?

[5] See 21 U.S.C. 351 ("the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacturer of drugs to ensure quality, ...").

ICH Q7 expects dedicated production areas for highly sensitizing materials such as penicillins and cephalosporins because of the patient risk (e.g., anaphylactic shock to penicillin-allergic patients) from trace amounts of these compounds in other medicines (ICH Q7, paragraph 4.40).

For materials of an infectious nature or high pharmacological activity or toxicity, a risk-based approach should be used to determine appropriate containment measures, which may include validated inactivation, cleaning, and/or dedicated production areas (ICH Q7, paragraph 4.41).

While ICH Q7 does not define high pharmacological activity or toxicity, these characteristics are generally determined by evaluating relevant animal and human data collected during research and development. Important considerations in this evaluation of pharmacological activity or toxicity may include occupational exposure limit (OEL), permitted daily exposure (PDE), acceptable daily exposure (ADE), threshold for toxicological concerns (TTC), no observed adverse effect level (NOAEL) (ICH safety guidances; ICH E2E, section II.A.1 (2.1.1)), and the consequences of cross-contamination (ICH Q9, section IV.C (4.3)).

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

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, paragraph 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 (organizational) controls (e.g., cleaning, personnel flow, environmental monitoring, and training).

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

E. Process Equipment — Cleaning (5)

5.1: For dedicated equipment, is "visually clean" acceptable for verification of cleaning effectiveness, (i.e., no expectation for specific analytical determination)?

"Visually clean" may be acceptable for dedicated equipment based on the ability to visually inspect and sufficient supporting data from cleaning studies (e.g., analytical

determination to demonstrate cleaning effectiveness) (ICH Q7, paragraph 12.76). Equipment should be cleaned at appropriate intervals (e.g., time or number of batches) to prevent build-up and carryover of contaminants (e.g., degradants or objectionable levels of microorganisms) so that they do not adversely alter the quality of the API (ICH Q7, paragraph 5.23, section XII.G (12.7)).

5.2: Should acceptance criteria for residues be defined for dedicated equipment?

Yes. Regardless of whether equipment is dedicated or not, it is expected that acceptance criteria for residues be defined and that the equipment be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants. Intervals can be based on number of batches, product change-over, time, etc. (ICH Q7, paragraphs 5.22, 5.23, 5.24, 5.25, 8.50).

Cleaning intervals and acceptance criteria should be established based on an understanding of the process/reactions/degradation, taking into account solubility, potency, toxicity, etc. Establishment of acceptance criteria does not necessarily imply sampling and testing after every cleaning. Visual inspection of equipment for cleanliness is an expectation of ICH Q7, paragraph 5.21. Where validation data has confirmed effective cleaning, cleaning procedures should be monitored at appropriate intervals (ICH Q7, paragraph 12.76).

5.3 Is it expected that equipment cleaning time limits be confirmed in cleaning validation?

Yes. Equipment cleaning is addressed in two sections in ICH Q7. Although the cleaning validation (ICH Q7, section XII.G (12.7)) does not specifically address time limits for cleaning, ICH Q7, paragraph 5.21, indicates that the maximum time between completion of processing and equipment cleaning (dirty hold time) should be established by the company. This maximum established dirty hold time is the time period for which evidence is available to demonstrate that the equipment can still be reliably cleaned. This maximum established dirty hold time is confirmed during the initial cleaning validation and can be extended with appropriate supporting data.

Although ICH Q7 does not specify the need for time limits between equipment cleaning and use in the next process (clean hold time), ICH Q7, paragraph 5.21 does state that written procedures should include instructions for the protection of clean equipment from contamination prior to use and inspection of equipment for cleanliness immediately before use, if practicable.

5.4 Is it expected that campaign manufacturing be addressed in cleaning validation?

Yes. The cleaning validation section (ICH Q7, section XII.G (12.7)) does not specifically address campaign manufacture. However, ICH Q7, paragraphs 5.23 and 8.50 set forth the expectations that equipment be cleaned at appropriate intervals (e.g., time or number of batches) to prevent build-up and carryover of contaminants so that they do not

adversely alter the quality of the API. The appropriate interval is confirmed during cleaning validation.

5.5 At product changeover, are both visual examination and analytical testing necessary to verify that equipment is clean?

Appropriate cleaning validation verifies that the cleaning process is effective. During cleaning validation, both visual examination and analytical testing should be used to verify cleaning effectiveness (ICH Q7, paragraphs 12.72 to 75). Once the cleaning process is validated, routine monitoring of cleanliness of equipment at product changeover should include visual inspection (ICH Q7, paragraph 12.76). Frequency of analytical testing to verify ongoing effectiveness of the validated cleaning process is determined by the API manufacturer using a risk-based approach. In situations where the cleaning process is not yet validated, both visual examination and analytical testing are expected.

F. Documentation and Records (6)

6.1: What is meant by "completely distributed" in ICH Q7, paragraph 6.13, which states that "records should be retained for at least 3 years after the batch is completely distributed"?

For APIs with a retest date, ICH Q7, paragraph 6.13 states that records related to production, control, and distribution should be retained for at least 3 years after the API batch is "completely distributed," which is understood as the complete distribution of the entire batch of the API by the API manufacturer to the next party in the supply chain. In the case of APIs handled by agents, brokers, traders, distributors, repackers, and relabelers (ICH Q7, section XVII (17)), "completely distributed" refers to distribution of the received quantity of the batch of API.

The intent of ICH Q7 is that records be retained for the period of time that the API could be on the market in order to investigate any problems and/or product complaints. Based on accepted industry practice at the time ICH Q7 was written, it was not anticipated that a manufacturer would set a retest date longer than 3 years. However, the use of "at least 3 years" in this section of ICH Q7 covers longer record retention periods, which is in alignment with the basic GMP principle and/or regional requirements that records be retained for the entire period the material is available on the market.

It is good industry practice to consider retaining records for the period of time the drug product(s) in which the API was used may be available on the market.

6.2: Does a batch numbering system need to be sequential?

No, ICH Q7, paragraph 6.51 says only that batch production records should have a unique batch or ID number.

6.3: Who is responsible for the issuance of batch production records?

ICH Q7, section II.C (2.3) does not specify who is responsible for the issuance of batch production records (ICH Q7, section VI.D (6.5)) as long as the issuance process is described in writing and approved by the quality unit (ICH Q7, paragraph 2.21).

G. Materials Management (7)

7.1: Does the phrase "grouping of containers" have the same meaning in ICH Q7, paragraphs 7.20 and 7.24?

The phrase "grouping of containers" should be read in the context of each sentence. A grouping of containers refers to multiple containers physically secured by the supplier (e.g., shrink-wrapped pallet) usually intended for ease of shipment and reconciliation. ICH Q7, paragraph 7.20 is referring to incoming visual examination of materials before acceptance into the facility under quarantine.

The phrase in ICH Q7, paragraph 7.24, "grouping of containers (batches)" contains an additional word "batches" because this section is addressing establishment of batch traceability for the incoming material.

7.2: What is expected in terms of evaluation of suppliers of materials?

Different phrases are used to describe the expectation for evaluation of suppliers of materials (ICH Q7, paragraphs 7.11, 7.12, 7.31), including traders, if any.

ICH Q7, paragraph 7.12 states that all materials are purchased against a specification and from suppliers approved by the quality unit (ICH Q7, paragraph 7.31). Prior to approval of any supplier, an evaluation should be conducted using a risk-based approach (ICH Q9, Appendix II.5; ICH Q7, paragraph 7.31). More extensive evaluation is important for suppliers of those materials classified as "critical" (ICH Q7, paragraph 7.11).

7.3: What is meant by "full analysis" (ICH Q7, paragraph 7.31) on batches of raw materials to qualify a supplier?

A "full analysis" should include all tests specified by the user of the raw material in the regulatory filing. In cases where no filing is required, the full analysis should include tests in other formal written specifications issued by the user of the raw material (ICH Q7, paragraph 7.31). A raw material supplier's Certificate of Analysis (CoA) may not necessarily align with the user's specifications.

7.4: Are on-site audits required in the evaluation of suppliers?

No. An on-site audit is not required; however, an on-site audit could be a useful tool in

the evaluation of a supplier. A risk assessment of the material or the service provided can be used to develop an audit strategy and manage the ongoing evaluation of suppliers (ICH Q7, paragraphs 7.11, 7.31).

7.5: Which tests are considered to be identity tests?

For incoming production materials, identity tests and related methods should be used as described in the relevant sections of a pharmacopoeia monograph, in an approved regulatory filing, or in an in-house specification (including method/analytical procedure) (ICH Q7, paragraph 7.30). When available, a discriminating test should be considered for identification testing. The visual examination of a label or the material is not considered sufficient except in the cases described in ICH Q7, paragraph 7.32.

7.6: Is it possible to extend the expiry date or retest date of a raw material and what is the acceptable practice to determine how long it may be extended for?

Manufacturing and labeling of raw materials for use by API manufacturers is outside the scope of ICH Q7. For this reason, retest and expiry dates, as defined in ICH Q7, do not strictly apply to raw materials and may be used in a different manner by the raw material supplier. *Expiry date*, as defined in the Glossary (section 20) of ICH Q7, applies specifically to the API.

API manufacturers may re-evaluate (ICH Q7, section VII.E (7.5)) and then use a raw material after the expiry date or retest date, based on an appropriate scientific and risk-based justification (e.g., understanding of material attributes, testing, and stability). Similar justifications may be used to extend the date by which the material should be re-evaluated. It is the responsibility of the API manufacturer to ensure the raw materials are appropriate for the intended use at the time of use.

H. Production and In-Process Controls (8)

8.1: Can yield ranges defined for the first batch differ from latter batches within a campaign?

Yes. Differing yield ranges (ICH Q7, paragraph 8.14) may be described and justified in the manufacturing procedure/master batch record explaining the ranges (ICH Q7, paragraph 6.41). For example, the first batch in the series of production of batches of the same material (campaign) may leave residual material in the equipment, resulting in a low yield in the first batch and contributing to an increased yield in a subsequent batch of the campaign.

8.2: What is meant by "appropriate specifications [of each batch] prior to blending" (ICH Q7, paragraph 8.41)?

As a principle, no batches with out-of-specification (OOS) results should be blended (ICH Q7, paragraph 8.41). Blending is defined in ICH Q7, paragraph 8.40. Individual intermediate and/or API batches should demonstrate conformance with the filed specifications prior to blending. In regions or circumstances where there are intermediates and/or APIs that do not require filing, conformance with the release specification should be demonstrated.

I. Packaging and Identification Labeling of APIs and Intermediates (9)

No Q&A.

J. Storage and Distribution (10)

10.1: What is meant by "APIs and intermediates can be transferred under quarantine to another unit under the company's control..." and is this applicable to contract manufacturers?

ICH Q7, paragraph 10.20 states "APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place."

The second sentence in ICH Q7, paragraph 10.20 describes transport situations that are not considered distribution. It provides for physical movement (transfer but not release) of quarantined material to another unit. This unit can be on the same site, be on a different site (within the same company), or be a contract manufacturer (see final paragraph below).

The goal of transfer under quarantine is to allow transportation and testing in parallel. Material that is transferred under quarantine is not to be used for further processing until all testing and quality review is complete and the material is released by the quality unit as defined in ICH Q7, paragraph 2.22.

This provision for transfer under quarantine is included in ICH Q7 for situations where a company is shipping APIs or intermediates from one unit to another and has both (1) the need to expedite the shipping and (2) the material management system in place to prevent use of the material before full release. Examples of circumstances where transfer under quarantine may be necessary include extraordinary supply chain requirement(s) (e.g., short shelf-life), and materials with a lengthy time frame for required test(s) (e.g., some microbiological tests).

With appropriate oversight as described in ICH Q10, section III.G (2.7), including a written agreement as described in ICH Q7, paragraph 16.12, and appropriate ongoing

controls, a contract manufacturer may be considered a "unit under the company's control." There is a joint responsibility for both parties to clearly justify and document the need to transfer the unreleased intermediate or API and to ensure appropriate control is maintained to prevent use before full release.

K. Laboratory Controls (11)

11.1: What is expected in terms of impurities for APIs extracted from herbal or animal tissue origin (ICH Q7, section XI.B (11.2))?

In cases where the API itself is the extract from an herbal or animal tissue preparation, all constituents of this extract (concomitant constituents) might be considered to be part of the API. Therefore, a production process-related impurity profile (except, for example, solvents used in the process) would generally not be expected. However, for all APIs derived from herbal or animal sources, tests and limits for possible contaminants originating from these sources (e.g., pesticides, mycotoxins, viruses, herbicides, elemental impurities, and wrong species) should be established, based on a risk assessment.

In cases where herbal or animal sources provide material that is further processed to yield a chemically defined API, all constituents other than the API are considered impurities. In this situation, the API manufacturer would be expected to establish an impurity profile as well as an API release specification that would include impurity limits.

In any case, it is the API manufacturer's responsibility to establish batch release specifications for APIs to ensure that they are safe and of high quality, consistent with appropriate regulatory requirements, applicable compendial specifications, and regional expectations (ICH Q7, paragraph 11.21; ICH Q9; ICH Q11).

11.2: In cases where an API test method is changed, which method should be used for stability studies already in progress?

The company should decide and justify the decision of which method to use. All test methods for stability studies (ICH Q1A) should be validated and demonstrated to be stability indicating prior to use (ICH Q7, paragraph 11.51).

Any changes to stability test methods should be documented. Applicability of the changes to the existing stability studies should be assessed and may require filing in accordance with regional requirements for postapproval changes (ICH Q7, paragraph 13.11).

11.3: When is it acceptable for an API manufacturer to extend an API retest date (ICH Q7, section XI.F (11.6))?

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 the manufacturer 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.

11.4: What is meant by "completely distributed" in ICH Q7, paragraph 11.71, which indicates reserve/retention samples should be retained for 3 years after the batch is completely distributed by the manufacturer?

"Completely distributed" refers to the distribution of the entire batch of the API by the API manufacturer to the next party in the supply chain. It should be noted that this 3-year retention of reserve/retention samples applies to all parties that physically process or repackage the API (ICH Q7, see Glossary (section 20) for definition of *manufacture*).

The intent of ICH Q7 is that samples be retained for the period of time that the API could be in the market in order to investigate any problems and/or product complaints. Based on accepted industry practice at the time ICH Q7 was written, it was not anticipated that a manufacturer would set a retest date longer than 3 years. It is a basic GMP principle that reserve samples be retained for the entire period the material is available on the market. For example, if a company sets a retest date of 5 years and the API is completely distributed immediately after manufacturing, it is not intended that the reserve sample be destroyed before the 5-year retest date is reached.

11.5: Why does ICH Q7 permit the use of a packaging system for reserve/retention samples that is "more protective than the marketed packaging system" (ICH Q7, paragraph 11.72)?

Unlike stability samples, the purpose of the reserve/retention sample is not to represent the quality of the batch in the market place but to allow future evaluation of the quality of the original API batch (e.g., in evaluation of potential counterfeits). Therefore, reserve/retention samples may be stored in packaging (and conditions) that better preserve the original state of the API.

L. Validation (12)

12.1: Is the lifecycle approach to process validation acceptable for APIs under ICH Q7?

Yes, ICH Q7 does not preclude the lifecycle approach (ICH Q7, paragraph 12.10; ICH Q10; ICH Q11).

12.2: **Can the range of a process parameter be expanded based only on a process deviation(s)*?***

No. However, information from the investigation into a process deviation(s) can be used to support expanding the range of a process parameter. Additional work and studies are normally needed to adequately demonstrate that the expanded range for the process parameter consistently produces API of the necessary quality (ICH Q7, paragraphs 2.16, 12.11, 13.13).

12.3: Would additional process validation studies be needed to support a change in the source of an API starting material?

Any change in the API starting material should be assessed for impact on the API manufacturing process and the resulting API quality (ICH Q7, paragraph 7.14). Additional validation studies of the API process may be warranted if the change in the API starting material is deemed significant. In most cases, validation would be expected for a different source of the starting material unless otherwise justified (ICH Q7, paragraphs 12.1, 13.13).

12.4: Is a retrospective approach to validation still acceptable?

Prospective validation is normally expected for processes introduced since the publication of ICH Q7. The concept of retrospective validation remains acceptable as an exception for existing, well-established products prior to the implementation of ICH Q7 (ICH Q7, paragraph 12.44).

If regulatory discussions redefine a step as critical, which had previously been considered noncritical, a protocol describing retrospective analysis of data together with the commitment for concurrent or prospective validation may be an option.

Regardless of the type of validation, the quality system should confirm the ongoing robustness of the process (e.g., product quality review).

M. Change Control (13)

13.1: Who is responsible for notifying the drug product manufacturer about relevant changes in API manufacturing?

Each party in the supply chain is responsible for transferring information related to quality or regulatory changes to the next customer in the supply chain. The intention is that the information is transferred along the supply chain to the drug product manufacturer in a timely manner (ICH Q7, paragraphs 13.17, 17.60).

N. Rejection and Reuse of Materials (14)

14.1: Should rejected materials be stored under physical and secure segregation?

ICH Q7 does not specify a need for physical and secure segregation. Both paragraphs 4.14 and 10.11 of ICH Q7 include the provision for the use of alternative control systems for storage of rejected material. Whatever control system is used, the purpose should be to prevent the unintentional or unauthorized use of the rejected material (ICH Q7, paragraphs 7.44, 10.11, section XIV.A (14.1)).

14.2: Does the definition of* expiry date *in ICH Q7 preclude the rework or reprocess of an expired API?

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 XIV.B (14.2)) or rework (ICH Q7, section XIV.C (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.

14.3: Is validation expected for the recovery of material from mother liquor?

It depends. Recovery of material(s) from mother liquor is a process, and the need for validation should be assessed as for any other process step (ICH Q7, paragraph 14.40). Recovery of material from mother liquor in any process step that must be controlled within predetermined criteria to ensure the API meets its specification is, by definition, a critical process step and should be validated. For example, recovery of API from mother liquor would be considered a critical process step and should be validated (ICH Q7, paragraphs 12.11, 12.12, 14.41, 14.43 — see Glossary (section 20) for definitions of *critical*, *materials*, *mother liquor*, and *validation*).

O. Complaints and Recalls (15)

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?

Yes. After the release of an API for further use, any identified quality defect should be investigated and addressed according to the API manufacturer's complaint system or equivalent (i.e., nonconformance, deviations, etc.) (ICH Q7, paragraphs 15.10 to 15.12). Where equivalent systems are used, such defects should be categorized in a manner that

provides clear visibility that the defect was discovered after being released by the API site.

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"?

No, provided that no portion of the batch left direct control of the company for sale or use. The return must be clearly visible in the API site's quality system as a return triggered by the API manufacturing site so this fact is clear in quality system trend reporting and in the product quality review (ICH Q7, paragraphs 2.50, 15.13, 15.14).

P. Contract Manufacturers (Including Laboratories) (16)

16.1: Does ICH Q7 preclude a contract manufacturer's independent quality unit from performing the main responsibilities as described in ICH Q7, paragraph 2.22?

No. The original intent of section II.B (2.2) was to distinguish the main responsibilities (e.g., batch record review, review of nonconformances and investigations, sampling, testing, release or rejection of intermediate or API) of the independent quality unit from other departments within a company.

Contract manufacturers are expected to have an independent quality unit that meets the responsibilities defined in ICH Q7, section II.B (2.2) for all activities performed.

Given the potential complexity of outsourcing contract manufacturing arrangements, GMP responsibilities should be clearly defined between both parties in detail in a written agreement (ICH Q7, paragraph 16.12). However, the overall responsibility for API quality must not be delegated.[6]

16.2: Which outsourced activities are covered by ICH Q7?

In the context of ICH Q7, contract manufacturing is the outsourced activity. The term *outsourced activities*, as defined and described in ICH Q10, section III.G (2.7) and Glossary (section VI (5)), aligns with the description of *contract manufacturer* in ICH Q7, section XVI (16).

ICH Q7 defines *manufacture* as "all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls."

[6] See 21 U.S.C. 351 ("the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacturer of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.").

"Related controls" include any activities or services necessary to support production (e.g., maintenance, calibration). ICH Q7 applies to any activities performed by the original manufacturer or the company that is performing the activity on behalf of the original manufacturer.

16.3: What is meant by "where subcontracting is allowed" (ICH Q7, paragraph 16.14)?

Subcontracting as used in ICH Q7, paragraph 16.14 refers to the contract acceptor further contracting out a specific activity to another party (third party). This should only be done when the written and approved contract, as described in ICH Q7, paragraph 16.12, specifically allows for such subcontracting. Even when subcontracting is allowed, the original contract giver should approve specific subcontracting before it occurs as stated in ICH Q7, paragraph 16.14.

Q. Agents, Brokers, Traders, Distributors, Repackers, and Relabelers (17)

17.1: What does ICH Q7 mean by "agents, brokers, traders, distributors, repackers, or relabelers"?

Regardless of what terms are used in different regions, ICH Q7 applies to all parties in the supply chain after the original API/intermediate manufacturer to the drug product manufacturer, in order to maintain the integrity, traceability, and transparency of the supply chain (ICH Q7, section XVII.A (17.1)).

17.2: Could a distributor of an API engage a contract manufacturer for production steps?

No. If a distributor (ICH Q7, section XVII.A (17.1)) of an API contracts out production steps (e.g., drying, micronization, milling, or sieving), then the distributor becomes a manufacturer and is subject to the entirety of ICH Q7.

This provision includes, but is not limited to, appropriate written agreements as stated in ICH Q7, paragraph 16.12 defining responsibilities of each party. In addition, these contracted production steps must be described in registration documents, applications, or equivalents per regional requirements.

17.3: Is it acceptable to replace the original label, which contains the information of the original manufacturer?

Any relabeling operations are considered manufacturing by definition (ICH Q7, Glossary (section 20)) and should be performed under appropriate GMP controls (ICH Q7, paragraph 17.40). With appropriate justification, manufacturers including repackagers and relabelers may replace the original label, so long as information about the original manufacturer is provided to the customers (ICH Q7, paragraph 17.61) and the traceability of the supply chain needs is maintained (ICH Q7, section XVII.B (17.2)). The new label

should contain information as per ICH Q7, paragraphs 9.42, 9.43. However, distributors should not remove an original label, but only add additional labels.

17.4: Who is considered to be the original manufacturer of the API for purposes of the Certificate of Analysis (CoA)?

The CoA should document the original manufacturer to support traceability throughout the supply chain (ICH Q7, sections XI.D (11.4), XVII.F (17.6)).

The original manufacturer would be the facility where the final purified API/intermediate is produced. Further physical processing (e.g., drying, micronization, milling, sieving) of an API would not make the manufacturer performing such operations the original manufacturer. All authentic CoAs, including those of the original manufacturer, should be available (ICH Q7, paragraph 17.20).

R. Specific Guidance for APIs Manufactured by Cell Culture/Fermentation (18)

18.1: Does ICH Q7 expect validation for viral removal/viral inactivation steps for biological/biotechnological products?

Yes. According to ICH Q7, paragraph 18.51, viral inactivation/removal steps are considered critical for some processes (e.g., cell lines of human and animal origin) (ICH Q5A, section 1). Parameters for validation should be established in accordance with ICH Q5A, Q5D, and Q6B.

Due to the potential for contamination (ICH Q5A, Section 2.B), viral inactivation studies should be performed in a separate and typically smaller laboratory facility (ICH Q11, section 7.2) and not in a clinical or commercial manufacturing facility.

18.2: Do ICH Q7, paragraph 18.14 and section XVIII.B (18.2) apply to classical fermentation and biotechnology?

For "'classical fermentation," the text from ICH Q7, paragraph 18.14 "…*this guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing*" refers to "classical fermentation" and not to the "biotechnology fermentation/cell culture." Although the entire ICH Q7 guidance does not apply prior to the introduction of cells into the classical fermentation process, as shown in Table 1 of ICH Q7, section I.C (1.3), an appropriate level of GMP controls suitable for cell banks should be established.

For "biotechnology fermentation/cell culture," ICH Q7, section XVIII.B (18.2) on "Cell Bank Maintenance and Record Keeping" applies specifically to biotechnology fermentation/cell culture because ICH Q7 starts with the maintenance of the working cell bank (ICH Q7, section I.C (1.3), Table 1). Although for biotech products the entire ICH Q7 guidance does not apply prior to the maintenance of the working cell bank, an

appropriate level of GMP controls suitable for cell banks should be established. See also ICH Q5B, ICH Q5D.

S. APIs for Use in Clinical Trials (19)

19.1: Is it permitted to use the same equipment to manufacture materials to be used in preclinical and clinical trials?

Yes, as long as operations are conducted under GMP conditions according to ICH Q7, including the establishment of effective cleaning methods, safe residue limits, and appropriate containment measures (ICH Q7, section XIX.C (19.3)).

T. Glossary (20)

20.1: Are the terms* deviation *and* nonconformance *synonyms?

No. However, they are related. The term *deviation*, as used in ICH Q7, refers to a "departure from an approved instruction or established standard" that may or may not have an impact on the quality of the material. *Nonconformance* refers to a status as a result of a failure of the material to meet specifications or appropriately established standards that has impacts on the quality of the material (ICH Q7, paragraphs 2.50, 14.30, Glossary (section 20)).

ANNEX: Q&As LINKED TO THE RESPECTIVE SECTIONS/PARAGRAPHS OF ICH Q7

Sections of ICH Q7	1: Introduction	2: Quality Management	3: Personnel	4: Buildings and Facilities	5: Process Equipment	6: Documentation and Records	7: Materials Management	8: Production and In-Process Controls	9: Packaging and Identification Labeling of APIs and Intermediates	10: Storage and Distribution	11: Laboratory Controls	12: Validation	13: Change Control	14: Rejection and Re-use of Materials	15: Complaints and Recalls	16: Contract Manufacturers (including Laboratories)	17: Agents, Brokers, Traders, Distributors, Repackers, and Relabelers	18: Specific Guidance for APIs manufactured by Cell Culture/Fermentation	19: APIs for Use in Clinical Trials	20: Glossary	Other ICH Guidelines
1. Introduction – Scope																					
1	1.3																				Q11 Q5B Q5D
2	1.2																			20	
2. Quality Management																					
1		2.13																			
2		2.13 2.22									11.12 11.10					16.10				20	
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5		2.50																			Q10
6		2.50 2.51																			Q9
3. Personnel																					
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4. Buildings and Facilities – Containment																					
1				4.40 4.41																	E2E Q9
2				4.42																	Q9
5. Process Equipment – Cleaning																					
1					5.23							12.76 12.7									
2					5.21 to 5.25			8.50				12.76									
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6. Documents and Records																					
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9. Packaging and Identification Labeling of APIs and Intermediates																					
10. Storage and Distribution																					
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Sections of ICH Q7	1: Introduction	2: Quality Management	3: Personnel	4: Buildings and Facilities	5: Process Equipment	6: Documentation and Records	7: Materials Management	8: Production and In-Process Controls	9: Packaging and Identification Labeling of APIs and Intermediates	10: Storage and Distribution	11: Laboratory Controls	12: Validation	13: Change Control	14: Rejection and Re-use of Materials	15: Complaints and Recalls	16: Contract Manufacturers (including Laboratories)	17: Agents, Brokers, Traders, Distributors, Repackers, and Relabelers	18: Specific Guidance for APIs manufactured by Cell Culture/Fermentation	19: APIs for Use in Clinical Trials	20: Glossary	Other ICH Guidelines
11. Laboratory Controls																					
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5											11.72										
12. Validation																					
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13. Change Control																					
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14. Rejection and Re-use of Materials																					
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15. Complaints and Recalls																					
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18. Specific Guidance for APIs Manufactured by Cell Culture/Fermentation																					
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2		1.3																18.14 18.2			Q5B Q5D
19. APIs for Use in Clinical Trials																					
1																			19.3		
20. Glossary																					
1		2.50												14.30						20	

REFERENCES

Except where otherwise noted, the following documents are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page.

ICH E2E *Pharmacovigilance Planning*

ICH Q1A(R2) *Stability Testing of New Drug Substances and Products*

ICH Q5A *Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*

ICH Q5B *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for the Production of r-DNA Derived Protein Products*

ICH Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products*

ICH Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

ICH Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*

ICH Q8(R2) *Pharmaceutical Development*
Part I: Pharmaceutical Development
Part II: Annex to Pharmaceutical Development

ICH Q9 *Quality Risk Management*

ICH Q10 *Pharmaceutical Quality Systems*

ICH Q-IWG Training Material for ICH Q8/Q9/Q10 available on the Internet at http://www/ich/org

ICH Q11 *Development and Manufacturing of Drug Substances*