
ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE



GMPs for APIs:

“How to do” Document

Interpretation of the ICH Q7 Guide

Version 16
(Update July 2022)

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(Revised chapters in this Version are highlighted in blue)

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Chapter 1 Introduction

1.1 Objective

Historical Background

When the initiative was taken by PIC/S at the Canberra meeting in September 1996 to draft a globally harmonised Good Manufacturing Practices (GMP) guide for the Production of Active Pharmaceutical Ingredients (APIs), the recommendation was made that this should essentially be a “what to do”, rather than a “how to do” document.

After that initiative the International Conference on Harmonisation (ICH), which consists of the three major pharmaceutical regions of the world - USA, Japan and Europe - took the topic on board. The ICH established an Expert Working Group (EWG) which membership was due to the importance of the topic extended beyond the three regions to WHO, PIC/S members, India, China and OTC and Generic industry representatives. The EWG, of which CEFIC APIC was a member of, has compiled the 'GMPs for APIs' Guide within 2 ½ years' time. The document was finalised by November 2000 and is now at the stage to be implemented within the three regions.

Purpose of the Document

This document was written by experts from the European Industry (CEFIC APIC). It is essentially an interpretation of “how to” implement the ICH Q7 Guide based on practical experience. Other relevant publications (e.g. ISPE Baseline Guides, other ICH Guidelines) were taken into account and references included (if applicable with indication of the version at date of publication of the “how to do” document).

This document does not intend to provide an exhaustive list of “how to” comply with the above-mentioned requirements and recommendations. It does however provide examples of commonly applied solutions and practical assistance on how requirements and recommendations can be met and /or interpreted.

Industry should avoid needless paperwork and administrative burden. As indicated in the Q7 document the focus should be - for the benefit of the patient - on identifying the critical controls and procedures that assure the quality of the API. Therefore, sound scientific judgement should prevail when setting up a quality system incorporating GMP.

Finally, APIC/CEFIC cannot guarantee that adhering to the principles laid down in this document will consistently result in trouble free inspections. Adoption of the guidance given will however provide both industry and regulators with a much greater confidence in the quality of global bulk active pharmaceutical ingredients manufacture.

The word « should » is extensively used in the final version of the ICH Q7 Guide. It indicates requirements and recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that can be shown to provide at least an equivalent level of quality assurance. Hence, « should » does not mean that because it is only a «should», and not a «must», then this requirement does not have to be met.

This document is meant to be a “living document” to describe current practice and to help with the implementation of the GMP Guide for APIs. Suggestions and/or

questions from industry or regulators to CEFIC APIC (<http://apic.cefic.org>) are welcomed. These will be discussed regularly by the industry experts and clarifications and improvements incorporated into the document.

Regulatory Requirements

Companies should be aware that the regulatory filing requirements might differ from the application of GMP as defined by Q7. There may be cases where more information may be required by regulatory authorities, but inspections for compliance with the Q7 Guide should only cover the GMP relevant steps.

1.2 Regulatory Applicability

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1.3 Scope

API Starting Materials

Companies are responsible for proposing the API Starting Material(s). This is one of the most significant changes proposed in the ICH Q7 document. The technical and quality groups should work closely with regulatory groups to ensure no disagreement occurs on the proposed API Starting Materials. Ideally the registration of New APIs will start from the API Starting Materials defined from a GMP perspective. However, based on current regulatory requirements it is likely that the regulatory authorities will require further information on API Starting Materials where only one or two synthetic steps exist between the API starting Material and the API or where the API Starting Material is an API itself.

The companies should review the synthetic process of each API and based on technical and quality assessments define what are the significant structural fragments beyond which the GMP standards defined in ICH Q7 should apply. In general, the source of the API Starting Materials is not the major factor.

The regulatory authorities may also require further details for late stage API Starting Materials, though recent examples are known that in specific cases FDA has accepted final intermediates as API Starting Materials (e.g. the widely commercially available substance 6-APA for the manufacture of semi-synthetic penicillin's)

Guidance on How to Define API Starting Materials

The APIC Q11 Q&A Task Force developed a decision tree that was incorporated in the ICH.Q11 Q&A document available in the link below.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11IWG_Step4_QA_2017_0823.pdf

Chapter 2 Quality management

2.1 Principles

Among GMP other aspects, such as quality systems, environmental controls, and safety, are necessary to be taken into account in order to be in compliance with regulations. Business efficiency and continuous improvement are needed to be competitive. Therefore, GMP compliance should be incorporated into an overall Quality Management Systems (QMS) as it is recommended in the EU GMP philosophy and ICH Q10 ensuring benefit to the patient.

Whether electronic or manual systems and records are used for all GMP requirements of ICH Q7, data integrity needs to be maintained.

The importance of an effective QMS on customer relations, continuous improvement, regulatory compliance, inspection readiness and supports ensuring supply of drug products to the market.

2.10	Company management should empower all appropriate organisational functions to apply the Quality policy and procedures. Assignment of clear Roles & Responsibilities for duties and decision making is the basic rule and can be achieved by e.g. process descriptions including principles of RACI (Responsible, Accountable, Consulted, and Informed) and decision trees. Delegated responsibilities should be documented, training given to relevant personnel and periodically re-training
2.11	A clearly defined QMS (as defined in ICH Q10) integrating API GMP requirements, should be documented, implemented and described e.g. in the Quality Policy approved by quality management and a system should be in place to deploy the quality policy throughout the organization.
2.12	Site Master File could be used to document the requirements of the Quality System (e.g. Eudralex vol. 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Explanatory notes on the preparation of a Site Master File, Part III or PIC/s PE008)
2.13	For the release of APIs there is no need for a “Qualified Person” (pharmacist) as defined by the European GMP Guideline (EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use) unless required by a specific law of the EU member state. The responsibilities for quality duties (e.g. process and control review, validation, change control, equipment qualification, batch documentation review, batch release, regulatory compliance, auditing, deviation handling, OOS treatments and complaint

	<p>investigation) should be clearly assigned to one or more person(s) or function(s). The QU should be involved in many, if not all, of these issues.</p> <p>If the QA and QC department are separated units the roles and responsibilities of each unit must be clearly described and approved by the management.</p>
2.14	<p>Release of raw materials and intermediates meeting the specifications and with no critical deviation identified (for internal use only) by Production is acceptable, provided QU has approved specifications and test methods. Production personnel should be adequately trained for these duties, the training recorded and all equipment used qualified and calibrated at regular intervals. The QU, as part of their responsibility for batch release, has the right to review all test results and data.</p> <p>APIs and intermediates (for use outside of the control of the company) have to be released by a designated person of the QU. Deputy(s) for such designated person should be nominated and trained</p>
2.15	<p>All activities should be directly recorded at the time they are performed in legible documents like note-books, electronic records, etc., which are retrievable and traceable. ALCOA+ principles should be followed.</p> <p>Recording in non-traceable documents like a blank sheet of paper (re-writing afterwards into traceable documents) is not acceptable.</p> <p>Electronic documents and recording requires appropriate validation of the systems used (see chapter 5.4 and 6.1).</p>
2.16	<p>Documented explanations should be in place for every deviation. When deviations are considered critical, the QU should make sure that a formal investigation occurs, the findings should be recorded and, if defined, corrective actions should be implemented. See chapter 8.15 for a more detailed explanation.</p>
2.17	<p>The release of an API or intermediate does not automatically require that all corrective measures or actions identified in deviation investigations have to be completed in advance (e.g. corrective actions related to ongoing training, maintenance, process investigations).</p>
2.18	<p>As an example, a regular report system (e.g. periodical Quality Management review) should be made available to senior management.</p> <p>QU is responsible for informing management of acute occurrences (quality related complaints, critical deviations, recalls, etc.). Senior management should review and endorse any recommendations and ensure that appropriate resources are made available.</p> <p>Quality Key performance indicators <u>should be implemented</u> to evaluate and ensure continuous quality improvement of the systems and processes.</p>

2.2 Responsibilities of the Quality Unit(s)

2.20	<p>Quality Unit (QU) should be responsible to implement and maintain the quality system as per the applicable guidelines such as ICH, FDA, PMDA, etc.</p> <p>QU duties may be delegated (exceptions see 2.22) to other departments/functions provided there are systems in place to ensure that the QU has adequate control / supervision. Different levels of control depending on the nature of the activity are required by ICH: “make sure” (for example: put systems in place, verify by auditing, assign responsibilities), “be involved” (means personal involvement of the QU responsible) or “establishing” (QU issues a system or procedure on its assigned duties).</p>
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	<p>QU will be responsible for implementing a Quality Risk Management (QRM based on ICH Q9)</p> <ul style="list-style-type: none"> - QRM is applicable during design, development, manufacturing (that includes warehousing, packaging, testing and distribution) and all API related activities including regulatory. - A QRM approach at all stages of the product life cycle will provide both a proactive and reactive means to identify and control potential quality issues. The extent of QRM documentation, communication/escalation, mitigation and review needs to be commensurate with the level of risk to product safety, efficacy, quality and regulatory compliance. - Each department owner of a process should be responsible for conducting pro-actively Risk Assessments in order to identify areas and actions that could pose a threat to the effective implementation of that process. Use of a cross functional team is recommended in performing the risk assessments. <p>A Procedure must be in place with the intention to assure the consistency of a Quality Risk management application including:</p> <ol style="list-style-type: none"> a) Risks are evaluated, assessed and managed b) Risks are escalated whenever necessary c) Decisions are taken using a defined process d) Documentation is developed and maintained. <p>Different Risk Assessment tools can be used but all are based on following principles: Examples of tools can be consulted in the ICH Q9 guideline, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf</p> <ol style="list-style-type: none"> i) The evaluation of the risk to quality should be based on scientific knowledge and ultimately be linked to the protection of the patient ii) The level of effort, formality and documentation of the quality risk management should be commensurate with the level of risk iii) Each company should install a risk register. The register should list and track all key risks as perceived by the organisation and summarise how these have been mitigated. There should be a clear reference link to the risk assessments. A management process should be in place to review risk management and support escalations if necessary. This might be incorporated in the quality management review process. iv) The QRM does not obviate to comply with regulatory requirements v) The QRM must be integrated throughout the product lifecycle vi) Once initiated the QRM process must continue being used for events that could impact original QRM decisions
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2.22	<p>The batch production records of critical (Reference to critical see Glossary) steps (a step could be the entire unit operation, e.g. conversion of the final intermediate to the API or a single parameter such as temperature control at an earlier step) including laboratory records have to be reviewed by the QU, whilst the review of all other steps may be delegated (ICH Q7, section 6.71)</p>

There should be a system in place defining what changes are likely to “impact intermediate or API quality” (ICH Q7, section 6.71). Nevertheless, any change has to be evaluated and communicated.

Stability data for intermediates are only required if they are intended to be sold (for reference see sections 11.60 in ICH Q7 and in the How-To-Do), but there isn't the need to apply a full stability program as described in ICH Q1a and Q1b documents. In many instances, a retest of the material prior to use or shipment is sufficient to demonstrate that the product is still meeting its specifications. (However, it is recommended to derive some data during the development phase or during validation to support storage periods of intermediates during campaign production or storage of left-over between two campaigns). For details see also chapter ICH Q7 section 8.21.

For delegate quality, related activities other than the ones listed in ICH Q7 section 2.22 the QU should demonstrate oversight (e.g. internal audits, trend reports, quality reviews, etc.).

2.3 Responsibility for Production Activities

2.30	Although related with Drug Product an additional support for the assignment of quality related duties to Production can be found in "EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4 part I chapter 5: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use."
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2.4 Internal Audits (Self-Inspections)

2.40	<p>Internal Audits (Self Inspections) are a valuable management tool to evaluate if the company is in compliance with the principles of GMP and additional requirements of the company which are integrated in the QMS. A procedure should in place specifying the requirements to perform internal audits (e.g. auditors, qualification and requalification, independence of the auditors, audit related documents preferably in a uniform template). The compliance assessment should be made by trained auditors, experienced in auditing skills and recruited from various departments of the company or performed by a qualified sub-contracted organization.</p> <p>A regular internal audit plan should be defined which can include the frequency based on a risk assessment, department, topics, audit team assigned, schedule, etc.</p> <p>The frequency as well as the compliance status of the area to be audited may vary from half a year to three years, and the rationale behind the frequency should be documented.</p> <p>Any change to the approved schedule should be justified and documented. APIC advice that all ICH relevant topics / applicable are challenged at least every 2 years.</p> <p>Quality Audit Teams (QAT) composed of normally 2 persons are recommended, however (depending on the focus of the audit) recruiting of additional experts (e.g. engineers, micro-biologists etc.) could increase audit efficiency. QU can be represented in a team, but not always taking the lead. The QAT should be responsible for co-ordinating activities such as follows:</p> <ul style="list-style-type: none"> • Assure the audit is performed as per the schedule • pre-audit meetings for the QAT • identifying major areas of concern and preparation of questions (questionnaire)
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	<ul style="list-style-type: none"> • collecting historic information such as deviations, changes, complaints, previous internal audit reports • issuing the agenda and distribution to the Auditee in due time • co-ordinating the activities of the QAT • summarising the findings in a close out meeting • issuing the audit report within a predefined period (usually 30 business days), on the basis of the close out meeting • QAT and QU should agree on the corrective measures or improvements and timelines to implement defined by the audited area and if required to inform the management (major non-compliance findings) <p>Follow-up and potential effectiveness to be performed by QU.</p> <p>All participants in the QAT should have the commitment from the management to use the specified time for preparing, performing and reporting the internal audit. Also un-announced audits or spot checks should be considered besides the “normal” audit programme.</p> <p>The internal Audit Report as well as the Follow-up Report should be kept confidential unless mandatory by the inspection authority.</p> <p>All (Internal) Audit Reports should be made available for the management, and the findings discussed. Management is responsible to initiate necessary corrective actions and investments.</p> <p>If the API manufacturer is at the same time the MA holder for the final drug product, there is an expectation that the finished product QP has access to all internal audit reports.</p>
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2.5 Product Quality Review

2.50	<p>The major objective of the Product Quality Review is to evaluate the compliance status of the manufacture (process, packaging, labelling and tests) and to identify areas of improvement based on the evaluation of key data.</p> <p>Product Quality Reviews (see 12.60) should assess the requirement for revalidation as part of the Continuous Process Verification program as per the current guidelines on Process validation (FDA and EMA). Product quality reviews should not be solely performed by QU personnel. It is important that other departments, like Production, Engineering, Maintenance, Purchase, etc. are also involved. QU is held responsible for the release and approval of the final report.</p> <p>To ensure that key data is reviewed it is essential for each production process to identify the critical in process controls, CPPs, Critical Material Attributes and critical API (or relevant intermediate) test results (CQAs). Statistical evaluation of the above parameters should be used to indicate the consistency of the process or to assess potential trends in the quality of the API itself.</p> <p>Ideally the critical parameters are identified in the development report prepared prior to process validation but may also be based on experience for well-established processes.</p> <p>Statistical tools can be used to establish key performance indicators.</p>
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	<p>Where the data concludes that there is a drift in process capability, actions should be determined to evaluate the causes and improve performance in the forthcoming review period.</p> <p>The review of all batches which fail to meet specification and the review of critical deviations should look specifically at recurring causes and identify appropriate actions to reduce the frequency and improve performance.</p> <p>Common causes for batch failures and recurring deviations are (this list should not be regarded as complete):</p> <ul style="list-style-type: none"> • Equipment not functioning correctly or in need of maintenance or replacement. • Inadequate batch instructions or training of operators. • Process parameters so tightly defined that the equipment is not capable of routinely achieving the acceptance criteria. • Inhomogeneous product or inadequate sampling procedures. • Poor quality raw materials or lack of control of raw material suppliers. <p>The impact of changes (see chapter "Change Control") introduced to the processes or analytical methods should also be carefully evaluated to look for any direct affect on the critical test results <u>and the process validation status. The impact of cumulative changes, not just the individual impact of a given change, should be considered when reviewing the impact of changes during PQRs.</u></p> <p>In a similar way, any trends in the stability monitoring program should be reviewed against changes introduced to the processes or analytical methods. Any trends indicating deterioration of product which could affect the retest period or expiry date of the API should be identified and an investigation into the causes should be performed.</p> <p>The status of quality related returns, complaints or recalls should evaluate the adequacy of corrective actions and any trends which require further investigation.</p>
2.51	<p>Based on the Product Quality review a list of clearly defined corrective actions and recommendations should form the basis of the objectives for the product in the forthcoming period. This should include the possibility of process improvements in order to keep the process under control and its validation status.</p> <p>Senior management should be involved in reviewing the recommendations and in providing the necessary resources and priorities to ensure the corrective actions and recommendations are implemented.</p>

Chapter 3 Personnel

General Remarks

Company management must encourage and recognise excellence. Staff must understand how they can influence quality, GMP compliance and contribute to improvement.

Staff at all levels must be competent and be effectively managed.

Management is responsible for promoting and maintaining the quality culture such as by monitoring of the Quality Culture Key Performance Indicators. Typical examples to monitor Quality Culture KPI are:

- Gemba walks.
- Present 1 or 2 topics to operators (catch attention) related to quality incidents happened recently.
- Operators are given the chance to follow customer audits and questions raised during the audit.
- GMP catch of the week valued.
- "Reward" continuous quality improvement proposals.

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3.1 Personnel qualifications

3.10	<p>Verification of the presence of an adequate number of personnel could be challenged by evaluation of the timely handling of quality related systems (deviations, CAPAs, complaints,...) and/or workload backlog in the Quality Unit, Production, Engineering, Maintenance,...</p> <p>Appropriate education means that the academic level/qualification, and professional (soft) skills should be defined for each job profile. This education should be supplemented by training and/or experience in the particular tasks to be performed.</p> <p>APIC advises each company to establish a system (e.g. competence matrix) for all employees as a tool to manage the adequate number of properly qualified personnel</p>
3.11	<p>It is stated in section 3.11 that the responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.</p> <p>This can be accomplished either in a generic way for a group of personnel e.g. warehouse personnel or operators in chemical production.</p> <p>For persons having a more specific responsibility, e.g. supervisors, process engineers, it might be more proper to have individual responsibilities laid down for instance in a function/job description.</p> <p>A possible way of indicating this is to use a matrix in which the responsibilities are defined. Another way of doing it could be the use of separate columns in a process flow chart indicating which unit or function (person) is responsible for what action.</p> <p>Another way of defining responsibilities is within the quality management system documentation - either in terms of which functions are responsible for activities or which personnel undertake specific tasks. Mixture of any of these can be used so long as the quality critical responsibilities defined in Section 2 are suitably documented.</p>

	<p>Job descriptions or function descriptions should identify the main purpose, role dimensions, outputs/responsibilities, reporting details and required competencies. These should be reviewed regularly.</p> <p>Function/job description should be signed (paper based or electronic) for acknowledgement at least by the employee and his/her manager or a designated person in the organisation</p> <p>In order to assure accuracy, the function/job description should be periodically reviewed, and updated if applicable, as per internal organisational procedure</p>
3.12	<p>Training should range from basic "induction" training through to job specific training. Employees should receive initial GMP awareness training as well as more focused training (e.g. document management for those involved in document control functions.) As a common practice <u>GMP refresher training should be conducted at least annually according to an approved plan.</u> The topics related to the GMP refresher can be based on: department specific items, new guidelines, GMP hot topics or driven by the performance review of the Quality System.</p> <p>Qualification of trainers can be based on education, training and/or experience and it should be documented.</p> <p>Before an employee is allowed to sign for execution of a particular GMP activity without supervision he/she should be qualified by education or should have received appropriate training.</p> <p>Training records should indicate the</p> <ul style="list-style-type: none"> • names of the people trained, • subject of training in keywords, • date and duration of the training, • name of the trainer, and • signatures of trainer and trainees <p>If procedures are revised or newly released the need for appropriate training, and assignment who needs to receive the training, should be assessed by the direct responsible and documented in the quality system.</p> <p>Effectiveness of training and trainers performance can be verified by direct (e.g. testing, questionnaire) and/or indirect means (e.g. individual observations, periodical assessment (usually annual), interview with supervisors, internal audits or root cause investigations pointing to human errors).</p> <p>Contractors from external companies that perform on site GMP related activities should be GMP qualified or should be trained in the same way as described above. Documentation of this training/qualification should be available.</p>

3.2 Personnel Hygiene

<p>The intention of this chapter is to protect personnel as well as products.</p> <p>People not trained in the departmental hygiene and gowning procedures can only enter the department if accompanied by an authorized, trained person.</p>	
3.20	<p>Personal hygiene should be practised by all staff as well as external people (contractors, visitors, consultants and inspectors).</p> <p>Periodical medical examination, according to the company's health care policy, is advised.</p>

3.21	<p>The type of protection garments to protect the materials from contamination at each chemical operation should be given in production instructions. These instructions must be written in a controlled document and should be followed.</p> <p>A process should be in place to avoid cross contamination before performing open activities on different products (e.g. changing overall, wear an extra overcoat, change gloves, change shoe covers, change hair and beard covers if appropriate....)</p> <p>The use of clothes with top pockets should be avoided to exclude the possibility of materials falling out while performing activities at open(ed) equipment.</p> <p>Wearing jewellery should be avoided.</p> <p>The use of make-up should be avoided at final stages of API manufacturing.</p> <p>For aseptic or sterile API manufacturing the Personnel hygiene requirements are described in the Annex 1 of the Eudralex Part I vol. 4</p>
3.22	<p>At the minimum gloves should be used when performing activities with potential product contact and product contact surfaces.</p>
3.23	<p>Manufacturing control rooms (computer room to control the processes) are considered part of the manufacturing area's (and usually have direct access to the manufacturing area). Eating, drinking, chewing and the storage of food is not allowed.</p> <p>When a manufacturing building has offices clearly separated from the manufacturing areas (e.g. by a corridor) like meeting rooms and personal offices, this is not subjected to restrictions.</p> <p>If the company allows smoking it should be in dedicated areas clearly separated from the production area.</p>
3.24	<p>It is each employee responsibility, engaged in GMP activities in direct contact with materials, to report illness, infectious disease or open lesions on the body exposed surface to inform the supervisor to allow assessment of associated risk.</p>

3.3 Consultants

3.30	<p>See ICHQ7 Q&A Chapter 3. Question 2</p> <p>If consultants are to be used they need to be evaluated, qualified and approved. The evaluation level should be risk based and related to the level of tasks to be performed.</p> <p>The review and final approval of any GMP document issued by the consultant (e.g. validation/qualification protocols and reports, SOPs) should be under the responsibility of the company's Quality Unit.</p>
3.31	<p>These records should be maintained in accordance with the company document retention schedule</p>

Chapter 4 Buildings and Facilities

4.1 Design and Construction

It is important to realize that API manufacturing plants are designed and constructed in various different ways depending on the chemistry, the nature of the API, the location of the plant (country, climatic region), GMP philosophy of the individual company etc. Also, it is obvious that existing ("old") plants and "state of the art designed" (new) plants are expected to be very different in design and construction. It was for this reason that the EWG did not give detailed instructions on the design and construction of API plants. However, both types ("old" and "new" plants) should comply with the principles of this chapter; however, they might be approached in a different way.

The design and construction of "new" plants reflect usually the increase of GMP understanding and principles which has been taken place in the API producing chemical industry during the past years. The ISPE's Baseline® Guide Volume 1, Active Pharmaceutical Ingredients (June 2007) is well known as a useful reference. It should also be noted that all literature references made in this ISPE guide (especially references to air handling systems / requirements) reflect U.S. standards which may differ from European requirements. Each individual company has to decide on the necessary requirements based on their business, quality and processes.

It is expected that compliance with this chapter for "old" plants (in which APIs and intermediates have been produced for many years and which have been frequently inspected by the health authorities in conjunction with various applications and marketing authorisations) can be partially achieved by organisational measures (SOPs), but to comply with Q7 8.52 it may be necessary to upgrade existing plants to give the required level of protection.

A "gap" – analysis to identify potential risks is a suitable method to establish additional measures (design or organisational) to bring "old" plants into compliance. Also appropriate requalification is required.

In order to perform the "gap" – analysis, Quality Risk Management (applying ICH Q9) at all stages of the product life cycle will provide both a proactive and reactive means to identify and control potential quality issues. This includes the implementation of a Quality Risk Management (QRM) for facilities design and construction.

- QRM for new GMP facilities, renovations and /or major upgrade to existing facilities starts at the planning phase. Based on the specific intended use of the areas and the defined critical process parameters by process step. These parameters shall include environmental requirements to be considered in the facility design as well as microbial control as required by the finished dosage form.

- During Design phase QRM tools should be used to identify modification (increase or decrease) of the requirements. Specific risks to be considered in this QRM exercise include:

- a) Particulate contamination
- b) Cross-contamination
- c) Microbial contamination
- d) Product mix ups
- e) Environmental conditions

- The results of the QRM exercise should be applied to develop and justify the facility design in relation with following:

- a) Required controls to maintain and monitor appropriate environmental process parameters
- b) Prevention of product microbial contamination, particulate contamination and cross-contamination

- c) Adequate flow of personnel, material and product
- d) Gowning/Degowning locations and requirements
- e) Room design and surface finishing
- f) Environmental protection and control.

4.10	<p>An increase of product protection is expected from early steps to the final API, more attention should be given in areas where open handling of the API, without further purification, is performed (e.g. drying, milling, weighing, packaging etc.). to add like the finishing of the room should be improved.</p> <p>The infrastructure should be designed, operated, cleaned and maintained to avoid contamination and mix-ups of raw materials, intermediates and the API. The organization should conduct a risk assessment based on the organization's intended use of the infrastructure to identify areas in which the API is at risk for contamination from deficiencies in buildings and/or facilities (e.g. operational areas physically separated from technical areas). The risk assessment should consider the following at a minimum to identify where the API is at risk from contamination:</p> <ul style="list-style-type: none"> a) Location of the operations (e.g. inside, outside) b) State of repair of the building and facility, c) Suitable size, construction and location, d) Ability to maintain a suitably clean building and facility environment, e) Operations that can affect the material quality, and f) Presence of airborne contaminants, especially highly sensitizing or toxic substances. <p>Where existing controls to minimize the risks of API contamination are not considered effective then additional measures should be documented and implemented.</p> <p>The ISPE November/December 2008 white paper https://ispe.org/sites/default/files/attachments/public/Nov-Dec-2008.pdf on the briefly open concept is advised.</p> <p>In principle, there are two options to achieve this goal: Open systems (products are handled temporarily in the open environment) or closed systems.</p> <p>If open systems are applied, a product could be exposed for a short period of time (e.g. sampling from a vessel, change of a container during discharging of a centrifuge etc.) or for a long period of time (milling, weighing and packaging operations, open filtration, discharging of a tray dryer etc.). This should require different levels of protection. For short term exposure additional procedures may be necessary (e.g. "Only one operation with exposure to the environment at the same time", "Appropriate clothing requirements for the personnel", etc.) to minimise potential contamination.</p> <p>For long term exposure, a suitably installed (e.g. according to ISPE Baseline Guide "Commissioning and Qualification" March 2001) and well-maintained air handling system could ensure the necessary protection.</p> <p><u>Some other precautions include:</u></p> <ul style="list-style-type: none"> • Spatial separation • protecting equipment during open product handling (e.g. covering, glove boxes, isolators etc.) • Design of piping (should <u>not be</u> located directly above open manholes, discharging devices etc. unless appropriate protecting measures are in place • Filtering of process gases and solvents
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	For closed systems in general no additional protection is necessary. The integrity of a closed system is not compromised by sampling operations provided appropriate measures are taken to prevent contamination.
4.11	<p>This specific requirement is of particular importance in multipurpose manufacturing areas. Examples for the manufacturing area are:</p> <ul style="list-style-type: none"> - Adequate space for materials (in transit). - Separated rooms for cleaning and storage of dirty and cleaned mobile equipment, spare parts and auxiliary tools is advised. - Physical protection between dirty and cleaned equipment <p>...</p>
4.12	<p>Reactors, fermenters, crystallisers, distillation columns, tank farms, storage containers or other closed equipment may be located outdoors, provided there is no need to protect the material from weather influences.</p> <p>Also, not permanently installed equipment (e.g. bulk containers, etc.) may be stored outside if additional measures to adequately protect the material are provided. Examples are:</p> <ul style="list-style-type: none"> - Shelter or protective roof - Pest control - Valves (including vents) are closed. - Protection caps on every inlet/outlet <p>...</p>
4.13	<p>Sometimes (especially in “old” plants) crossing of material or personnel flow cannot be avoided. In this instance additional organisational measures (SOP’s) should be implemented based on risk assessment, to ensure prevention from mix-ups and contamination. Examples are:</p> <ul style="list-style-type: none"> - Cleaning materials outer package before entering in the manufacturing areas. - Only one material handled in the same area at the same time. - No simultaneous transit of clean and dirty mobile equipment in the same area at the same time. - Auxiliary tools (clean or dirty) protected from the environment by means of plastic bags. - Appropriate gowning (see 3.21) - ... <p>New plants should be designed to provide separate flow of materials and personnel.</p>
4.14	<p>Other control systems can be computerised material management systems.</p> <p>Quarantined and released materials (raw materials, intermediates, APIs) could be stored in the same area (but no mix-ups on pallets etc.), provided their status is clearly indicated and/or traceable and procedures are in place to avoid unauthorised use (labels, computer status).</p> <p>Separate production areas are required for certain materials (see 4.4)</p> <p>For safety reasons, separate storage facilities may be required for classes of materials with hazardous and /or unstable chemical or physical attributes.</p>
4.15	Preferably liquid soap should be used.

	On final step gloves should be sanitized times to times, whenever micro requirements are defined
4.16	Analytical measurements (e.g. conductivity, pH, density, N-IR, chromatographic methods) need not necessarily be carried out in separated (laboratory) areas, e.g. in case of online analyses.

4.2 Utilities

4.20	<p>Only applicable for critical utilities which are commonly identified by the manufacturer as part of design during risk assessment of his processes. In general, only utilities which are in direct contact with the product (e.g. steam distillation, compressed air or nitrogen blanketing), or in contact to the inner surface of equipment.</p> <p>When using compressed air with direct product contact it is recommended to use oil free systems. In case oil needs to be used it should be food grade.</p> <p>The frequency and level of monitoring will depend on the use of the utility and may range from daily (e.g. even online) monitoring to spot checks (e.g. intervals up to once a year) on systems which are carefully maintained. The frequency of testing may be reduced once the company has justified this based on historical data.</p>
4.21	<p>Appropriate only if open systems are used (reference to 4.12). If open systems are used the ISPE's Baseline® Guide Volume 1, Active Pharmaceutical Ingredients (June 2007) provides useful information (reference to 4.1).</p> <p>Opening windows and doors is not considered an appropriate practice to achieve adequate ventilation.</p> <p>A risk based design is appropriate in an API manufacturing site with increasing environmental protection from Starting Material to final API taken into account the final dosage form.</p>
4.22	<p>Appropriate measures may be e.g.:</p> <ul style="list-style-type: none"> - selection of suitable filters (and appropriate change of them) - mixing of returned air with fresh filtered air - Clean up time / recovery room time (e.g. verified by particle measurements) on product change; including cleaning or changing of filters. - If air is humidified during the recirculation process the water quality must be justified (e.g. when micro specs to the API are required).
4.23	<p>Although it is required that permanently installed pipework should be identified (with the content and direction of the flow), this requirement should be limited to pipework dedicated to a particular medium. Other permanently installed pipework (e.g. connection panels for various solvents and reagents) could be generically identified (e.g. 1R22 to 0R14, a connection between two different reactors). Drawings of pipework should be updated every time.</p> <p>Identification of the content of the pipeworks could also be done by means of pipes labelling standards.</p> <p>Pipework for waste (gases, liquids) should be designed and appropriately located to avoid contamination (e.g. vacuum pump, cyclones, scrubbers, common ventilation pipework from reactors/vessels). Back pressure (non-return) valves can be considered as can swan necks. Draining valves should be installed at the lowest points. During design, methods of cleaning of pipework should be considered.</p>

4.24	If needed drains should be sanitized at regular intervals avoiding microbial growth, such sanitization may be simply conducted through use of an approved and appropriate cleaning agent and it should be documented.
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4.3 Water

4.30	<p>Develop a documented rationale as to what water quality is sufficient and/or which measures may need to be taken to ensure API quality.</p> <p>Suitability depends on the stage in manufacture, intended route of administration or the nature of the API. Documented evidence should be available that the water used does not negatively affect the product quality.</p>
4.31	<p>Incoming city water quality should be monitored on a routine basis to verify that it meets the WHO requirements for drinking (potable) water and the results should be documented by the API manufacturer.</p> <p>Additional in-house testing and monitoring of the process water should be considered by the manufacturer according to a predefined and approved plan (including point of use, testing, sampling and frequency) against predefined specifications that ensure a safe and sound quality of the API (usually meeting guidelines for potable water, unless otherwise justified).</p> <p>Potable water may be even more suitable for use than treated (softened) water due to measures taken to limit microbial growth.</p>
4.32	<p>It is the responsibility of the manufacturer to define the specifications of water and to monitor its quality (according to pre-approved plan) to achieve the API critical quality attributes.</p> <p>The assessment should take into account the final purification step(s) of the API and the finished dosage form administration.</p> <p>The EMA “Guideline on the quality of water for pharmaceutical use” should also be considered during this assessment (if the API or the resulting finished dosage form is distributed within the EU).</p>
4.33	<p>Qualification/Validation principles (chapter 12) and Change Control (chapter 13) need to be applied.</p>
4.34	<p>In this case, water quality should be also monitored on a routine basis to verify its quality (according to pre-approved plan) and the results should be documented.</p> <p>Microbiological testing should consider both suitable online monitoring (e.g. TOC) and point of use testing. Endotoxin testing is carried out offline and the LAL-test is an option, but recommended for API to be used in parenteral formulation</p>

4.4 Containment

4.40	<p>HVAC systems of this dedicated facilities should not impact other materials, processes and buildings (e.g. exhaust away from the inlet of the HVAC system of buildings used for other materials).</p>
4.41	<p>The EMA guideline “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities” should be considered.</p>

	https://www.ema.europa.eu/documents/scientific-guideline/guideline-setting-health-based-exposure-limits-use-risk-identification-manufacture-different_en.pdf .
4.42	<p>For certain APIs (see 4.40 and 4.41) it may be appropriate to use dedicated or disposable clothing and dedicated equipment including tools for maintenance within the area. Specific clothing requirements should apply to all personnel e.g. maintenance staff, visitors, etc. Facilities for changing clothes or showering should be considered and special hygiene practices should be applied.</p> <p>See question 4.1 and 4.2 on buildings and facilities of ICH Q7 Q&A of chapter 22 of this document.</p>
4.43	<p>For highly toxic non-pharmaceutical materials for example pesticides and herbicides you may refer to local authorities for local requirements.</p> <p>The comments made on 4.14 should be applied.</p> <p>If the same building is used for the storage of other materials (raw materials, intermediates and APIs), completely segregated areas can be accepted for the storage of closed containers of highly toxic non-pharmaceutical materials. Open product handling of these highly toxic non-pharmaceutical materials is not acceptable.</p>

4.5 Lighting

4.50	<p>Should comply with National regulations (e.g. Health & Safety).</p> <p>When the design of the lighting of the area is insufficient to properly perform operations (e.g. visual inspection of cleaned equipment, reading of labels, ...) additional means should be made available.</p>
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4.6 Sewage and Refuse

4.60	<p>Disposal has to be performed according to National law. In order to prevent misuse, it may be necessary to ensure physical destruction, i.e. incineration of certain APIs, e.g. narcotics.</p> <p>Containers and pipes used for waste materials can be identified by means of:</p> <ul style="list-style-type: none"> - Color code - Labeling - Specific packaging - ... - Or a combination of the above
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4.7 Sanitation and Maintenance

4.70	<p>It has to be pointed out that there is a significant difference between a finished dosage form manufacturing environment (physical processes) and a chemical plant, where aggressive and corrosive reagents may be used. This significant difference should be considered in defining "clean condition". Level of cleanliness required may change from a closed to an open system, also depending on the stage of manufacture. The closer to the end product, the cleaner the production environment should be. Management should assign adequate resources to ensure a good state of cleanliness and maintenance in API facilities. Useful tools to evaluate/report the state of cleanliness and maintenance of facilities are:</p>
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	<ul style="list-style-type: none"> - Preventive maintenance - Process for notification of deficiencies (rust, leakage, chip paint, ...) - Internal audits - ... <p>Additional guidance may be found in the ISPE's Baseline® Guide Volume 1, Active Pharmaceutical Ingredients (June 2007).</p> <p>An appropriate pest control program is recommended to avoid pests to enter the manufacturing area's and to assist in maintaining the clean condition of the facility. It is recommended that the pest control program considers both crawling and flying pests.</p>
4.71	<p>Routine cleaning and pest control programs should be defined and documented. Cleaning and pest control programs (including frequency) would be approved by the Quality Unit.</p> <p>Accidental spills and its cleaning is recommended to be handled as an incident.</p> <p>Effectiveness of the cleaning and the pest control program should be verified and documented by the area responsible person.</p> <p>External contractors can be used for sanitation, facility cleaning and pest control activities. They should be trained in GMP and their responsibilities defined in a contract (see chapter 3.1 and 3.2).</p> <p>Defined areas for the storage of temporarily used equipment and its status (cleaned, identified and protected from the environment) should be available.</p>
4.72	<p>The use of rodenticides, fungicides, fumigating agents and cleaning and sanitizing agents should comply with the National regulations.</p> <p>It is not recommended to use these toxic materials in areas where open product handling occurs. If needed, its use should be approved by the Quality Unit.</p>

Chapter 5 Process Equipment

5.1 Design and Construction

5.10	<p>The ISPE baseline guide volume 5 "Commissioning and Qualification" gives a very pragmatic system to ensure that systems are "fit for purpose" which means adequate size, material compatible with the process, easy to clean and to maintain. This guide recommends undertaking an assessment to separate critical equipment from non-critical. An example would be that cooling water services should be designed according to Good Engineering Practice (GEP) while the temperature probe used for a critical processing parameter should be fully qualified (Qualification: reference to chapter 12.3) using an enhanced design review.</p>
5.11	<p>Materials of construction including the ones related with accessories (e.g. O-rings, gaskets, etc.) should be indifferent towards the process materials in order to minimise potential reactions of such materials (e.g. iron with salt solutions giving rust) to avoid formation of impurities that could adversely affect product quality. It also means that the materials should not shed extraneous matter into the process and they should not leach materials into the process. Some forms of polymer or filter cloths would be examples of this type of material.</p>

5.12	If equipment has been qualified over a narrow range and is capable of operation over a wider range then before use it should be re-qualified over the wider range at least under the process performance stage (Chapter 12.3 PPQ). Most manufacturers design equipment for use in multi-product facilities. From this perspective, it would be advisable to purchase equipment that has versatility and is able to cover a wide range of requirements. It should be ensured that the equipment is able to operate correctly for each particular process. (Reference: Chapter 12.3, PPQ). An example of this may be a temperature probe that can monitor temperatures over a range -20 to 150 °C but that can also be tuned to enable a reaction temperature of just ± 2 °C to be accurately monitored without the tolerance of the instrument being greater than the range.
5.13	Major Equipment can be identified using as built Pipe and Instrumentation Drawings (P&IDs) with pipes also identified in the plant as well with the content and direction of the flow.
5.14	An approved list of lubricants etc. can help to ensure that the correct materials are used. Each material should be reviewed for chemical compatibility and potential quality impact. The FDA webpage: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm can be searched for approved food grade materials. These can also be specified to equipment vendors during design of new equipment. Increasingly dry seals for agitators are being used to overcome this type of issue.
5.15	This statement particularly applies to the final steps and isolation of the API. For most chemical syntheses, this would be a safety requirement in any case. It needs to be stressed that there are no requirements for room specifications for non-sterile APIs at any stage of processing. It is prudent however to increase precautions as the final API step is approached. Early steps requiring materials to be charged in an open plant (inside) environment may also require controls but only for operator protection provided basic cGMP control is in place. See also Chapter 7.4 for additional advice for sampling activities.
5.16	As built drawings should be maintained and updated as part of change control and equipment re-qualification process. Failure to do this could lead to safety and quality issues.

5.2 Equipment Maintenance and Cleaning

5.20	A good preventative maintenance program is very important in reducing the number of equipment breakdowns that could cause impact upon product quality, schedule and maintenance costs. This is particularly important for critical equipment unit (including related accessories e.g. condensers, pipes, etc) that needs regular attention to prevent failure.
5.21 to 5.26	Documentation of completion of the cleaning procedure should include: <ul style="list-style-type: none"> - Who did and when - The cleaning parameters (e.g. temperature/cleaning agents/quantities/times) - The former product including batch number - Acceptance criteria (including change-over limits) - Sampling if applicable

See the APIC Documents "[Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants](http://apic.cefic.org) " for practical advice on this subject. (<http://apic.cefic.org>, "publications").

5.3 Calibration

5.30	<p>Many companies make the mistake of allowing engineers to classify any measuring device as a critical device. Each device should be reviewed to assess what the impact would be of failure or incorrect readings.</p> <p><u>Classifying instruments as:</u> critical GMP= CPP (critical process parameter) or CQA (critical quality attributes) controlling equipment, GMP = direct quality impacting, GEP = indirect or non-quality impacting.</p> <p>Undertaking this task will allow the critical measuring equipment to be very tightly controlled and not submerged by the vast numbers of instruments that are used within an API site. Many companies use outside agencies for calibration. The equipment user is responsible for ensuring that the outside agencies are dully qualified and competent to undertake the calibration to the appropriate standards. Periodic audits to the outside agencies should be performed including to the calibration records and procedures.</p>
5.31	<p>All calibrations independently of the criticality of the measurement should be performed against standards traceable to other instruments that are more accurate</p>
5.32	<p>As per document retention requirements in section 6.</p>
5.33	<p>A very good approach is to calibrate prior to start up (initial qualification stage) and then at defined intervals according to the history of calibrations built up with experience. A good idea when starting is to have regular reviews of such data to collect supporting data to define appropriate calibration frequencies (shortened or expanded, based on collected data and experience), re-evaluation periods etc. These reviews are also a very helpful tool to observe any trend and therefore to be able to react before instrument failure occurs.</p>
5.34	<p>A procedure should exist to ensure that instruments not meeting calibration criteria are not used. For this reason, tolerance ranges and calibrations should be appropriately selected for the process to ensure that non-impacting failures of calibration criteria are not routinely observed.</p>
5.35	<p>As mentioned the calibration of critical instruments must be appropriate to prevent unnecessary non-added value investigations into minor failures that could never impact upon quality.</p>

5.4 Computerized Systems

<p>Computerised systems have a very high profile and require an extremely thorough validation approach. It is an area of high inspector interest especially in what concerns to DATA INTEGRITY aspects of the systems (ALCOA + Principles, access control, audit trail, etc.)</p>	
5.40	<p>The validation extend should be based on a risk assessment analysis of each element of the system. Assessment system defined by the FDA, MHRA and/or ISPE guidance are also a very useful tool to use so that resources and effort are appropriately targeted on critical systems.</p>
5.41	<p>IQ and OQ of computer hardware and software are often treated entirely separately from equipment IQ/OQ. It may be very advantageous to combine the two especially when the two are intrinsically dependent or linked.</p>
5.42	<p>This is a very good approach in that commercially available software by the nature of economic viability and wide-scale usage will reasonably have determined whether the software is fit for purpose. The GAMP guidance is very useful in determining the testing requirements.</p>
5.43	<p>Basic security measures such as access control, audit trail and user passwords will enable most systems to operate in a compliant manner. Electronic date, time and user stamps are becoming more and more prevalent as industry becomes familiar with the requirement for audit trails. A common problem however is that some audit trails are poorly designed and do not allow searching on the basis of reason for change, date, operator etc. This area is a very significant area of interest for inspectors.</p>
5.44	<p>Similar requirement for all systems, procedures must exist so that personnel can be trained accordingly and these standard operation procedures have to be followed by the operators. This is a basic requirement of system validation.</p>
5.45	<p>Where a second operator is used it does not mean that the operator must watch the figures being entered just that the value should be checked. Double data entry where the system checks each entry against the previous entry to ensure there has been no transcription error. This has been found to be a very effective error reducing mechanism.</p>
5.46	<p>This is analogous to equipment logs. Again, some form of categorisation and system should be used to ensure that non-value added or non-quality impacting information is not being collected and investigated</p>
5.47	<p>Change control should be appropriate to the criticality of the system. GEP systems should not require quality review.</p>
5.48	<p>For GMP systems a backup system should be available. A server system with automatic back up is ideal but read only CDs can be as effective. It should be noted that it is very difficult to make local PC systems secure.</p>
5.49	<p>Digital readouts etc. can be documented manually or by use of chart recorders.</p>

Chapter 6 Documentation and Records

6.1 Documentation System and Specification

6.10	ALL data generated should follow ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available) principles
6.11	<p>Electronic, paper based or hybrid systems can be used to control the issuance, revision, approval and withdrawal of documents. The system in place should be managed in a controlled manner with QU oversight.</p> <p>The workflow of documents should be defined in a written procedure(s).</p> <p>If an electronic or hybrid system is used to control the issuance, revision, approval and withdrawal of documents the system should be validated and be in compliance with data integrity principles including audit trail.</p> <p>During the life cycle of a document if an update of its content is required, it should be documented. The revision history of the document shall be traceable over the retention period. Where electronic document management systems are used the details of the document history can be retained in the metadata and so does not have to appear on the document itself.</p>
6.12	<p>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.</p> <p>The following supporting documents should be retained for LC +1 year:</p> <ul style="list-style-type: none"> - clinical batches for an IND or NDA (see also chapter 19) - batches for bioequivalence testing - product development reports - development and validation protocols/reports of analytical test procedures - process validation protocols/reports - equipment IQ, OQ and PQ protocols/reports - supporting systems qualification and validation protocols/reports (e.g. utilities, computerised systems). <p>(for clinical trials and demonstration batches LC + 1 year should be considered)</p> <p>Training records should be retained indefinitely.</p> <p>Note: LC means “life cycle” of the product where shelf life is included. “Life cycle” means the process starting with the user requirements, continues through design, realisation, qualification, process validation and maintenance until the discontinuation of the product in the market.</p> <p>Electronic data should comply to the same record retention principles.</p> <p>Electronic data should follow the applicable regulations such as Eudralex Vol 4, Annex 11: Computerized Systems for the EU.</p>
6.13	Self explanatory. Note this has implications for electronic data in that companies must maintain the capability to read records when upgrading hardware or software.
6.14	<p>Paper-based systems</p> <p>Use of pencils for making entries in the documents is not allowed.</p> <p>No white out and no crossing out resulting in obliteration of an original entry that is subsequently corrected. No overwriting.</p>

	<p>Document a rationale for corrections unless it is clearly obvious (e.g. typo mistake). The date when the correction is made and the person who made the correction should be indicated.</p> <p>Electronic systems</p> <p>Audit trail should be available to trace corrections. See as a reference, e.g.:</p> <ul style="list-style-type: none"> - WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 4 – Guideline on Data Integrity - MHRA “GXP” Data Integrity Guidance for Industry - FDA Data Integrity and Compliance with drug cGMP. Questions and Answers Guidance for Industry - EMA Questions and Answers: Good manufacturing Practice - Eudralex Vol 4, Annex 11: Computerized Systems - PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments. - ISPE Records and Data Integrity GUIDE - APIC Practical Risk-based Guide for Managing Data Integrity
6.15	<p>Data should be secured by physical and/or electronic means against damage and loss (e.g. fire proof cabinets/rooms, scanning, ...). Accessibility, readability and accuracy of data should be ensured throughout the retention period.</p> <p>When physical records (paper-based or electronic) are stored in external (outsourced or within the same company) archives, a record retrieval period of 24 hours is generally accepted. For outsourced archives the record retrieval period should be specified in the Quality Agreement.</p> <p>“Regular back-ups of all relevant electronic data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically”. Quoted from Eudralex Vol 4, Annex 11: Computerized Systems</p>
6.16	<p>True copies should be generated by a verified process. See as a reference, e.g.:</p> <ul style="list-style-type: none"> - MHRA “GXP” Data Integrity Guidance for Industry - PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments. - FDA Data Integrity and Compliance with drug cGMP. Questions and Answers Guidance for Industry <p>Handling of electronic data should follow the applicable regulations such as Eudralex Vol 4, Annex 11: Computerized Systems for EU.</p>
6.17	<p>The level of detail in the specification should be based on the criticality of the material in the process and a defined control strategy (see ICH Q11 - Development and manufacture of drug substances Section 6).</p>

Item	Type of Specification
Raw materials (RM)	Specification is mandatory. Pharmacopoeia grade materials are not needed unless necessary to control the quality of the final API
API Regulatory Starting Materials	Specification is mandatory. More details are typically needed compared to RM (i.e. impurities control).
Intermediates	Specifications are required for intermediates if defined in the control strategy and are typically expected for isolated intermediates.
APIs	If compliance with a pharmacopoeial monograph is claimed then specification tests and limits should be aligned with the monograph unless variation has been accepted by the appropriate regulator. For non-compendial APIs refer to ICH Q6a. Additional specifications can be separately agreed with customers.
Labelling materials	Approved label specification is mandatory (including relevant parameters such as size, colour, pre-printed information). Control on the label content is described in section 9.3
Packaging materials	Specifications for primary and secondary packaging materials are mandatory.
Process aids including utilities (product contact materials)	If such materials are critical as per control strategy specifications are mandatory. Such specifications should be justified for example by alignment with public specifications (e.g. technical standards like PhEur, USP, ISO, EN etc.).
IPC	Acceptance criteria need to be established for every IPC test (unless the IPC is defined for informative purpose).
6.18	Handling of electronic data should follow the applicable regulations such as Eudralex Vol 4, Annex 11: Computerized Systems for EU and FDA Guidance for Industry Part 11, Electronic Records; Electronic Signatures

6.2 Equipment Cleaning and Use Record

6.20	A use log of all activities performed in the equipment is mandatory. The use log must be regarded broader than production only. It includes also maintenance, calibration, cleaning,... This documentation can be electronic or paper based, if electronic these should comply with sections 6.10 and 6.18.
6.21	For dedicated equipment, if the records of cleaning, maintenance and (re)use are included in the batch record, it may be recommended that this information is written on the first pages and that critical entries are reviewed by a second person. In case of equipment trains that are not changed during manufacturing, a plant or unit log instead of individual equipment records could also be applicable.

6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

6.30	The objective of this record keeping is to trace the above Materials back to the supplier's production records and trace forward until the API-batch delivered to individual customers in case of any failure occurring in the supply chain (supply chain integrity).
6.31	Most frequently a master label (included in the master batch record or in a dedicated archiving system) is approved and used, however the approved master of a label does not need to be a label itself but may consist of an approved set of relevant data used by or sent to a label printer. An extra label or a copy of the label should be added to the batch record to proof compliance with such master. If an electronic system is used for label generation and printing there is a need to prove that the original batch label can be retrieved at any time and under CFR part 11 compliance. Any label update needs to follow the change control procedure.

6.4 Master Production Instructions (Master Production and Control Records)

6.40	The review has to be performed by the appropriate people/functions. This may involve R&D, QC, Production, Engineering as well as SHE (safety, health, environment) departments. The Quality Unit should approve the master production instructions as stated in 2.22. All changes should be performed under the change control procedure.
6.41	Critical process parameters and critical steps should be identified in the Master Production Instructions. It is possible to use, at different production locations, different Master Production Records derived from the same basic recipe.

6.5 Batch Production Records (Batch Production and Control Records)

6.50	---
6.51	Under the API manufacturer's quality documentation system and with final QU approval
6.52	<ul style="list-style-type: none">• For deviation reports: see comments on 8.15• Identification of equipment: see comments on 6.21• Double signatures of performing and checking personnel: see discussion on witnessing under 8.12• Yields: see comments on 8.14• Labels: see comments on 6.31 For every printing of batch labels, the process for label verification and comparison with the master should be repeated.• Packing and labelling of intermediates is applicable for any separate storage of materials, e.g. batch production starting from warehouse stocks. It should include evidence that suitable controls have been applied to avoid mix ups and mistakes. Keeping a copy of intermediate labels as for final packaging is a possibility.• Status of the equipment before use
6.53	<p>An investigation has to be set up for every critical deviation. A SOP on investigations of critical deviations should define what is to be understood by critical. During the investigation the root cause (or the most probable cause) should be established and an impact assessment to other already produced batches should be performed to identify if they were also affected by the same deviation. This information should be documented in the investigation report.</p> <p>The use of the principles in ICH Q9 (Quality Risk Management) is recommended to classify critical deviations.</p>

6.6 Laboratory Control Records

6.60	<p>Graphs, charts and spectra can be added to the control record or can be stored separately. In the latter case, these documents should be easily retrievable.</p> <p>These documents should be signed and dated by the person who performed the test. A reference to the identification of the sample analysed should be included.</p> <p>The secondary review of the original records only needs to be done when the complete analysis of a sample of a batch has been performed. This review should be documented.</p> <p>If calculations are made using electronic systems (for example Excel spread sheet, LIMS) these should be validated.</p> <p>When an electronic system generates analytical data, these data are considered true and original data.</p> <p>Data integrity principles should be applied. See as a reference, e.g.:</p> <ul style="list-style-type: none">- WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 4 – Guideline on Data Integrity- MHRA "GXP" Data Integrity Guidance for Industry
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	<ul style="list-style-type: none"> - FDA Data Integrity and Compliance with drug cGMP. Questions and Answers Guidance for Industry - EMA Questions and Answers: Good manufacturing Practice - Eudralex Vol 4, Annex 11: Computerized Systems - PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP environments. - ISPE Records and Data Integrity GUIDE - APIC Practical Risk-based Guide for Managing Data Integrity
6.61	<p>Modifications of analytical methods should be subject to change control and considered for revalidation prior to introduction.</p> <p>There should be a system in place to avoid that equipment out of the calibration period is used.</p> <p>For stability testing of APIs see 11.5</p> <p>For OOS investigations see 11.15.</p>

6.7 Batch Production Record Review

6.70	<p>The procedure for the review and approval of batch records should include the list of items to be checked (see 6.72)</p> <p>“Established specifications” cannot always be limited to pharmacopoeia specifications, also additional in-house specifications could apply.</p>
6.71	<p>Critical process steps that should be reviewed by the quality unit are typically:</p> <ul style="list-style-type: none"> • Critical process parameters that impact on the critical quality attributes of the intermediate or API. • Packaging and labelling steps • Remarks/observations/incidents/deviations
6.72	<p>During a batch record review check for:</p> <ul style="list-style-type: none"> • missing records and out-prints • incomplete entries • illegible corrections • equipment maintenance, breakdown and replacement • valid calibrations and service intervals of test equipment (as a useful cross check to routine control of test equipment) In batch production review there is no need to ask for or seek verification of the calibration status of equipment. This is part of the ongoing QA system which would be expected to be compliant in routine cases. • reports on OOS-results • completeness of deviation reports (See comments 8.15) • impact of reported deviations on product quality

	<ul style="list-style-type: none"> • compliance with specifications, parameter ranges or acceptance criteria including tighter customer specifications Reference 12.5 Process validation program • Reference: 12.21 for batch release <p>Prior to the release of intermediates and API's process validation batches any constrains from the process validation protocol should be considered.</p>
6.73	<p>At the time of API release the QU should have a system in place to verify that the delegated responsibilities were performed correctly. This verification can be done risk based (instead of continuously performing a complete review) by using tools like internal audits, spot checks, A periodical complete review is recommended. Review of critical process steps cannot be delegated. See 2.22 and 6.71</p> <p>The QU is responsible to assure periodical re-training of delegated responsibilities is performed.</p>

Chapter 7 *Materials Management*

7.1 **General Controls**

All activities from receipt till approval or rejection of materials should be described in one or more procedures. Materials must be purchased against agreed specifications.

Companies should prepare a list of Starting Materials and critical raw materials based on good scientific rational and impact on the quality of the API. This list should be approved and controlled by the quality unit;

There should be differentiation between a critical raw material and a starting material. For a critical raw material a control strategy should be in place to assure the API meets its specifications (QCA) See also:

http://apic.cefic.org/pub/APIC_Position_Paper_on_API_Starting_Materials_Jan2014.pdf

All Suppliers (manufacturers and/or agents if applicable) of materials should be evaluated and approved by the quality unit. The evaluation should be risk based and can be based on but not limited to:

- historical experience with the supplier and reliability,
- a questionnaire,
- checking/comparing own analytical results (for e.g. three batches/shipments) with those on the suppliers Certificate of Analysis and / or
- an audit done by a person authorized by the purchasing company
- use test

Audits are not mandatory as per current GMP and should be considered on a case by case basis A documented risk assessment is needed to determine the necessity to perform an onsite audit as part of the supplier evaluation/qualification. Audits are a useful tool to understand the quality culture implemented at the supplier and to support the control strategy of the purchased material. If audits are used auditors should be trained in auditing techniques and have knowledge of the quality standards/expectations of the materials being evaluated. Other useful information can include the Quality Culture of the supplier within the industry and the availability of certificates such as ISO9001 certificates. The evaluation and approval process should be described in a procedure, taking into account some or all of these possibilities. This

includes the fact that the name and address of the manufacturer of a critical material must always be known and documented as part of the supplier approval list. A change of the source (e.g manufacturer or supplier) of a starting material and critical raw material should be handled according to the change control procedure.

7.2 Receipt and Quarantine

Before acceptance of incoming materials, the packaging should be checked visually. The materials should be sampled, tested and released. (exception is described in 7.32) Intercompany shipments can be accepted using a reduced testing program or accepted based on the CoA in case a control strategy is in place.

As long as the material is not released it must be held under quarantine; this can be realised in different ways e.g. labelling, separate areas or through a validated computer system. These systems or others may also be used to identify the status of the material.

7.22

Incoming stock materials should be released before mixing them with the existing stock. This new stock should get a new ID number. The system to assure traceability of the stored and used bulk materials should be described in a procedure. It is advised to periodically sample and test the current stock for compliance to the specifications. The frequency of periodical sampling and testing can be based on the frequency of use. In case the non-dedicated tanker has multiple compartments, each individual compartment should be sampled and tested before release to the main storage tank.

Non-dedicated tankers should be checked for cleanliness before use to prevent cross-contamination A cleaning certificate should be provided with each supply and is part of the product approval documentation. The availability of the cleaning certificate should be part of the incoming reception process of bulk deliveries in tankers.

The previous mentioned product on the cleaning certificate should be acceptable for the quality unit of the receiving company. It is preferred to archive the cleaning certificate together with the testing release documentation.

7.23 As in the factory, large storage containers and possible appendages should be identified appropriately.

7.3 Sampling and Testing of Materials

Sampling plans should be scientifically sound, preferably statistically based, appropriate to the material being sampled, easy to use and documented. The importance of obtaining a representative sample for analytical testing is critical. The quality/accuracy of the analytical data obtained is dependent on how representative the sample is.

Sampling plans must consider not only how the raw material is manufactured but the use and criticality of the material. As a consequence, sampling plans may be different for different materials, and grouping of materials in different sampling methods is commonly used. A risk based assessment approach can be used to support and justify the most appropriate sampling plan.

Examples of parameters which may be evaluated during a risk assessment are:

- Criticality of the material
- Manufacturing and supply process: manufacturer and/or agent controls
- Manufacturers/Suppliers quality systems
- Packaging controls
- Historical data
- Homogeneity

Manufacturing and Supply Process/Homogeneity

Knowledge of the raw material manufacturer's process is important in determining the appropriate level of sampling. Factors to consider are, whether the material has a final processing step that ensures the material is homogeneous and/or whether the manufacturer has homogeneity data for the current process of the concerned material. If the material is homogeneous then the need to sample from multiple containers and test a number of samples may not be required. Homogeneity data may be obtained from the supplier or generated in house. If it is not homogeneous (or knowledge is not available) then there is a risk. In this case the use of the material should be considered to determine the necessary level of sampling and testing for example top, middle and bottom of the containers. Take for example the scenario where a material that is not potentially homogenous with respect to water and the level of water in the material can impact downstream processing. If one container is used at a time in a process, then every container may need to be tested, but if all the consignment is used in one batch of the process then a testing of a composite of the batch to give a mean representation of the batch made up from all the containers may be more appropriate.

Knowledge of the raw material manufacturer's process is not the only information that is needed; subsequent packaging and handling operations should also be considered. For example, consider the scenario where a process produces homogeneous material product but downstream packaging or drumming introduces the potential to desegregate it - this would impact sampling plans.

Another factor to consider is if agents/repackaging operations are used in the supply chain. If agents are used then knowledge of their quality systems, operations and practices must be considered. For example, the risk from an agent or distributor that repackages a material is potentially greater than that of an agent who only holds and distributes the material in the original packages/containers.

Issues of homogeneity can usually be ignored for low viscosity liquids.

Supplier's quality system

Knowledge of the supplier's quality system is also important. Quality systems are used to support the quality and integrity of the product. Any reduced sampling plans should only be applied to vendors who have adequate quality systems as one of the major concerns for supplier evaluation is to consider the potential for product contamination.

An understanding of the process, facilities and potential for cross contamination needs to be known and considered. For example, if material is received directly from a manufacturer that only produces one product, then the risk of cross contamination is less than from a supplier using dedicated equipment in a multi-purpose plant. This in turn is less than from multi-purpose equipment. Consider the scenario where a solvent is manufactured in a dedicated facility, but is drummed in a multi-purpose one rather than a dedicated drum filling facility. For the latter, sampling of any drum should give a representative sample for testing but in the former scenario, if the drum filling order is known, sampling and testing of the first drum may provide more appropriate analytical data relating to potential batch contamination.

Review of the suppliers packaging and labelling controls is beneficial as this can be used to support review of the labelling of incoming deliveries as a system for identification purposes.

Information on the quality systems can be obtained via an audit of the supplier or via an appropriate vendor questionnaire. The questionnaire should contain the relevant questions to allow an assessment of the supplier's quality management system. Other information can support this for example ISO certification or confirmation of a successful regulatory audit.

Historical data

Previous quality knowledge of the manufacturer's/supplier's deliveries/other materials may be useful data to ensure an appropriate sampling plan is assigned. A review of OOS investigations and complaints can assist.

Criticality of the material

Critical process parameters of a process may be linked to a raw material parameter. This in turn may lead to a need for a sampling plan that ensures this parameter is tested to a different regime to that of the other materials quality attributes to ensure downstream processing is not impacted.

In theory, only after a thorough evaluation during the risk assessment process, reduced sampling and testing should be considered.

Even though it has no statistical basis, common industry practice is to use $\sqrt{n+1}$ (where n = number of containers) and is widely accepted in many situations if the material is homogenous. Other examples of sampling plans are BS 6001-1:1999+A1:2011, ISO 2859-1:1999, ANSI/ASQCZ1.4-1993, derivatives of $\sqrt{n+1}$ in WHO document, [http://whqlibdoc.who.int/trs/WHO TRS 929 eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf) (Annex 2 and 4).

Other considerations

If there is a quality issue with a raw material that may impact the sampling plan then increasing the sampling regime can be applied. This may include changing the number of containers to be sampled or even the sampling method for the material. As data becomes available that shows the preventative measures taken by the manufacturer/supplier are controlling the issue then a return to the normal sampling can be reinstated with appropriate justification.

If sampling could have an impact on the integrity of the material, for example hygroscopic substances, then less sampling should be considered. Co-shipment samples for release testing purpose or as retention sample may be acceptable on the conditions that:

- The supplier is qualified.
- Documented evidence that the sample is representative for the batch is available.
- Packaging, labelling and transportation means of the sample is described, traceable and agreed by both parties.
- Measures are in place to assure the material quality is not impacted during distribution. Preferably the co-shipment sample is delivered together with the material to best mimic the bulk material shipment conditions.
- A system is in place to periodically assess the co-shipment sample representativeness for the batch (except products mentioned in section 7.32)

Other practices can be considered like for example additional testing just before use. These scenarios should be justified and documented.

Processing aids, hazardous or highly toxic raw materials which are not sampled and tested before release should be evaluated as per ICH Q7 section 7.32. It should be considered to:

- Classify the raw material as “hazardous or highly toxic” when applicable,
- Get the manufacturer’s CoA for each delivery,
- Check the packaging and labelling to verify identity of incoming material (instead of testing),
- Have a written scientific rationale in place, and
- Optionally sample/analyse/verify at the moment of charging.

7.4 Storage

Materials should be stored in a way that the quality of the raw material cannot be negatively influenced taking into account light, time, temperature and humidity. Materials must be stored in compliance with the manufacturer storage prescription Sufficient space should be available in the warehouses to allow efficient movements without damaging the packaged materials as well as to allow for cleaning. It is good practice to store the material at sufficient distances from walls.

For pest control see section 4.7.

Definition of Rejection see ICH Q7 14.10.

OOS material with ongoing investigation and/or waiting for final disposition decision (for example reprocess/rework or destruction) should be quarantined

Materials that are identified for destruction should be stored in a separated restricted area to prevent un-intendant use of the material.

Systems like FEFO (First expired First out) and FIFO (First in First out) are normally used to control that the oldest stock is used first. If a supplier provides expiry dates for material FEFO should be applied, if no expiry date (but a retest date) is available FIFO should be applied

The system to assure that the oldest stock is used first can be paper based or electronic. Both are acceptable. Any process used need to be described in a procedure.

The floor of the warehouses should be easy to clean.

Materials stored in fibre drums, bags or boxes should be stored off the floor e.g. on wooden heat treated or plastic pallets. Materials (e.g. in steel drums) may be stored outside if their identification remains guaranteed and if the material is not adversely affected by such storage conditions. Before bringing the material into a controlled area and/or before opening these containers they should be cleaned appropriately.

7.5 Re-evaluation

Re-evaluation according to original specs should be applied.

sampling and testing can be reduced (e.g. 1 sample per lot number, non-stability indicating test like heavy metals not retested, ...) but this process and assignment of a new retest date needs to be described and justified in a procedure.

See also Chapter 6. Materials Management in the ICH Q7 Q&A chapter at the bottom of this document

Question 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?

Chapter 8 Production and In-Process Controls

8.1 Production Operations

8.10	<p>Weighing or measuring of raw materials should follow procedures designed to ensure accuracy and to avoid cross contamination.</p> <p>These may include:</p> <ul style="list-style-type: none"> • Specified weighing or measuring areas protected from the environment with controlled access. Dedicated areas may be necessary for certain raw materials based on toxicity. • Use of log books or registers to record the usage and cleaning of the weighing, measuring area. • Cleaning procedures for the weighing, measuring areas • Procedures to ensure that materials for different processes are not dispensed concurrently • Extraction systems to control dust or vapour exposure during dispensing • A range of appropriately scaled weighing or measuring devices should be available to ensure accuracy of weighing operations. The appropriate scales for specific weights or measures should be defined. • Flowmeters, for liquids, or weight belt feeder, for solids, may be appropriate for charging or for monitoring continuous production processes. • Critical weighing and measuring devices should be appropriately calibrated and traceable to certified standards. The calibration should be recorded and performed on a regular basis.
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	<ul style="list-style-type: none">• Regular checks and records by operational staff that balances are functioning correctly should also be considered. The frequency for these checks should be justified.
8.11	<p>Examples of suitable primary container for sub-dividing solids are</p> <ul style="list-style-type: none">• a plastic bag for smaller quantities or• plastic bags, liners inside rigid support, or• loading hoppers for quantities of solids. <p>Multi-use containers receiving sub-divided material (e.g. loading hoppers) should be clearly identified. Such equipment should be appropriately cleaned according to written procedures.</p>

8.12	<p>Companies should define the critical weighing, measuring or subdividing operations which should be witnessed or subject to an equivalent control to the minimum number General non-critical weighing or measuring of materials does NOT require witnessing. As it was seen in the step 2 ICH Q7 document it was intended that such weighing operations should be “supervised”, which would not have required the physical presence of a second person. However, the word “supervised” suggests that someone more senior in the organisation should carry out this task. To avoid this interpretation the word “witnessed” was chosen to indicate that anyone could carry out this check. However, it was not intended that this word should be used within the narrow legal sense of being physically present throughout the operation and a subsequent check of a second person would fulfil the requirement.</p> <p>A typical equivalent control that avoids the need for a second person is a recording system where all weighing or measuring operations are detailed. The critical weights or volumes should be confirmed at the end of the batch production.</p> <p>The final check by production that the identity and lot numbers of dispensed raw materials comply with the batch instructions may also include a check of the quantities or volumes of critical measurements These checks should be clearly defined in the operating instructions for each batch.</p>
8.13	<p>Companies should decide which operations other than weighing and dispensing could be considered critical and therefore should be witnessed or subject to additional controls. Examples are:</p> <ul style="list-style-type: none"> • Charging of critical raw materials. • Control of critical temperatures, pressures, times. • Point of crystallisation of API where this is critical to the control of polymorphs. • Operations that are critical (and thus subject to these controls) should be documented on the Batch Production Records and related documents.
8.14	<p>Variation in yield is a likely indication that a process is not performing to expectations. Therefore, investigation of variations in yields at defined process steps is intended not only to control variations in production efficiency but also to optimise process consistency and assist in assuring consistent product quality.</p> <p>The expected yield may be defined at designated steps for example key intermediates, the final step of synthesis of the API.</p> <p>When wet products or crude liquids are involved, it may be necessary to calculate the yield after analysis and determination of the percentage of expected product.</p> <p>In some cases, there could be significant batch to batch variations in yield due to different quantities of product remaining in enclosed equipment such as filtration or drying equipment. In these cases, monitoring of yield trends or averages over a range of batches may be more appropriate.</p> <p>Yield definition may also not be practicable in purification steps, continuous production processes or processes with multiple recycle streams (e.g. mother liquors). These processes instead may be assessed for example on a weekly or monthly basis.</p> <p>The important point is that companies should evaluate and document the likely yield expectancy and variability and decide what is the expected yield and the likely impact on quality.</p>

	<p>Once again there are advantages in defining critical process steps to ensure that the yield investigations are focussed on the steps likely to have an impact on product quality.</p>
8.15	<p>A deviation is defined as a departure from an approved instruction or established standard.</p> <p>The guidelines require that ANY deviation to the defined processing steps in the production records should be documented at the time the event is noticed. It may be useful to have an additional page in the production record to allow easy recording of unexpected occurrence or deviation to the standard instructions.</p> <p>Deviations need to be reported immediately. The responsible person decides – based on an approved procedure - which deviations are critical and require immediate investigation. The Quality Unit should review and approve the deviation records. The Quality Unit should verify the deviation classification and assure CRITICAL deviations with potential impact on API quality are completed and approved prior to batch release. (reference 2.22 and 6.72 ICH Q7).</p> <p>A critical deviation is defined as a departure from established critical parameters or a significant departure to standard operations which MAY affect the quality of the API or intermediate. Critical deviations should always be investigated and corrective/preventive actions identified. Corrective/preventive actions may be subject to change control procedures.</p> <p>A pre-defined time period for investigation closure should be defined in an SOP. A maximum of 30 calendar days is commonly used. At the time of an extension a new due date needs to be agreed based on an approved justification with the QU and the “next steps” need to be defined and documented in an intermediate status report.</p> <p>For critical deviations at the time of release at least the investigation report should be closed and the definition of the corrective/preventive actions should be defined.</p> <p>Where deviations recur on a regular basis the need for example to re-qualify equipment, retrain operators, redefine the process parameters or to implement other appropriate actions should be considered. The recurrence of deviations should be part of the assessment done during the Product Quality Review. See Section 2.5.</p> <p>Examples of deviations are:</p> <ul style="list-style-type: none"> • Incorrect charging of raw materials • Process parameters (temperature, pressure, vacuum,...) outside defined limits. • Operating instructions not correctly followed. • Breakdown of process equipment or failure of utilities. • Equipment out of calibration. • Production records not adequately completed. • Not planned alterations to defined production instructions • In Process Control Limits not achieved and production is continued. • Alternative production equipment used at short notice (emergency change). • Potential contamination of API, intermediates and raw materials • Any other unplanned event.
8.16	<p>Defining the process status of equipment is intended to assist the process operators and supervisors to properly control their operations and avoid the mis-use of equipment.</p> <p>In particular the following examples should be well controlled:</p>

	<ul style="list-style-type: none"> • The batch number and process in operation • The cleanliness status of equipment • Equipment under maintenance, Out of Service or Out of Calibration
8.17	<p>Colour coded labels for material for reprocessing or reworking may be appropriate. The Quality Unit should clearly identify material for reprocessing or reworking and ensure that the appropriate procedure for reprocessing or reworking has been approved before the production unit consider using these types of material.</p> <p>The appropriate control of materials requiring reprocessing or reworking could be quarantine (see 10.11), computer controlled, specific labelling, locking of equipment or other appropriate measures.</p>

8.2 Time Limits

8.20	<p>Examples of possible deviations of time limits for processing steps are:</p> <ul style="list-style-type: none"> • extended drying or distillation times beyond what is normally observed due to faulty equipment, • interruption to normal production due to external events e.g. fire alarm or power failure or public holiday. • Use of raw materials or intermediates beyond documented storage times.
8.21	<p>An appropriate storage area for intermediates held for further processing should be defined. The storage area should protect the materials from the risk of external contamination or cross contamination with other materials and from extremes of temperature and relative humidity.</p> <p>Intermediates which will be stored for any significant period should either be tested again prior to use or have a retest or shelf life period established.</p> <p>The retest or shelf life period can be determined by but not limited to:</p> <ul style="list-style-type: none"> • Bibliography. • Information of the manufacturer. • Based on the experience of the company when re-testing products that have been stored during a certain time. • A simple analytical check of material kept under standard storage conditions. (This does not need to comply with ICH Q1A) <p>Special care should be taken with the storage of wet intermediates, to assess the likelihood of degradation.</p>

8.3 In-process Sampling and Controls

8.30	The most common examples of in-process controls are: pH control, reaction completion, crystallisation, and batch drying checks. In these and other cases, the in-process control data assists with process monitoring.
8.31	The acceptance criteria are not intended to be specification checks unless there is a direct relationship with product quality.
8.32	This approval could be carried out as part of the master production instruction approval.
8.33	Any deviations from pre-established limits for critical in process controls should be investigated and reviewed by the quality unit.

8.34	<p>Sampling is required to be scientifically sound.</p> <p>Samples are used to monitor the process and the results of the sample predefines the disposition of the material being processed. The integrity of the sample predefines the integrity of the analysis.</p> <p>The importance of sample integrity should not be overshadowed by the focus upon the result.</p> <p>Scientific sound sampling procedures should be developed by considering the following issues:</p> <ul style="list-style-type: none"> • Sample size: at least enough to undertake check testing if designated a critical test requiring OOS investigation. • Sampling method: should be demonstrated to provide representative samples of the whole batch. Particular care is required for sampling of solids and slurries. Simple dip pipes can be used for homogeneous liquids while more complex systems including re-circulation loops may be used for slurries. Sampling of solids is best done from a falling goods stream. Sampling out of bags or drums should be done carefully to ensure representative samples obtained for particle size distribution and analysis when these parameters are critical. • Sampling procedure: should provide sufficient instruction to ensure that truly representative samples are obtained. Details should include flushing, re-circulation and cleaning of samplers (sampling equipment). <p>Particularly for critical steps and sampling of the API itself evidence should be available that the sampling methods allow a representative sample to be taken.</p> <p>Where there is a risk that the batch is not homogeneous for example tray drying of an API a blending step to improve homogeneity should be considered.</p> <p>Example: Although the sampling regime SQR of n+1 is a common but not the only practice within the industry we recognise that other statistical approaches can be suitable Root n+1 is scientifically sound - -it may not be statistically valid but it provides an acceptable point between sample every container and sample only one</p> <p>ISO 2859 Sampling procedures for inspection by attributes is an alternative reference.</p>
8.35	<p>Sampling tools should be controlled by a cleaning procedure and should be adequately stored when not in use to avoid contamination. Cleaning status of the sampling tools should be identified.</p> <p>Care should be taken to minimise the risk of external contamination during in process sampling. For example, in situ sampling probes should be considered when sampling the final API or protective covers should protect the area where the process equipment will be opened. As a minimum, the area around the sampling point should be well maintained with no evidence of flaking paint, rust, dust or other possible sources of contamination.</p> <p>Procedures should be in place to protect the integrity of in-process control samples, for example: flushing of in situ sampling probes to ensure a representative sample is taken.</p> <p>In process sample containers should be clean, clearly labelled with product name or code, date, time, batch number, step number, operator name, if relevant.</p> <p>Reference: ISPE Baseline BPC Guide Current version is called "ISPE Baseline Guide: Active Pharmaceutical Ingredients Second Edition June 2007.</p>

8.36	In-process tests that require OOS should be clearly identified/designated and these should be critical tests only. For these cases the level of investigation (in the lab, sampling, number of replicates) should be defined.
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8.4 Blending Batches of Intermediates or APIs

8.40	–
8.41	<p>As written the guidance on blending applies to both chemical and physical property specifications. Where the intention is that each individual batch should conform to both chemical and physical property specifications.</p> <p>Care should be taken when setting specifications for intermediate steps or for APIs not to include unnecessary limits if a further processing step e.g.: re-crystallisation as part of the process, milling or micronisation will result in product which complies with the final specifications.</p>
8.42	-
8.43	–
8.44	–
8.45	–
8.46	–
8.47	–

8.5 Contamination Control

8.50	Where significant carryover occurs between batches and particularly in the case of filter or dryer heels, it should be demonstrated that no unacceptable build-up of impurities or, where applicable, microbial contaminants is occurring (see 5.23 ICH Guide). This will also assist in determining the frequency of cleaning of equipment which is dedicated to the long-term manufacture of one product.
8.51	<p>A wide range of production facilities exist from modern multi-purpose facilities designed to minimise risk of cross contamination to older facilities which rely on procedural controls to minimise cross contamination.</p> <p>It is recommended that companies review existing facilities and define the controls required to minimise cross contamination particularly as the process moves to the final API isolation.</p> <p>Some of the risks which should be assessed are as follows:</p> <ul style="list-style-type: none">• Where more than one product is manufactured simultaneously in one production area or building strict procedures should be in force to avoid for example cross contamination or the misuse of raw materials and intermediates during processing operations.• Generally, charging areas should be clean and tidy with no evidence of for example flaking paint or rust, or dripping water from service pipework in the vicinity of the charge area.• Where intermediate is isolated in open production areas, adequate protection measures and distances should be maintained between equipment for different processes for example filters or dryers

8.52

These clauses have potentially wide impact on API manufacturers.

- Charging of solids and liquids at the final step of APIs should be controlled to avoid cross contamination.
- Solids loading systems which avoid opening of reactors to the environment may be appropriate for the final API.
- Segregation of the isolation areas for the final API including controlled access by personnel should be considered.
- Where the API is exposed to the external environment for example during sampling of the final reaction mixture, offloading of filters or dryers then building controls and procedures should be in place to avoid the risk of external contamination.
- No microbiological monitoring of isolation areas and equipment for APIs used in oral solid dosage forms is required unless a microbiological quality is specified.
- Classified Rooms, if applicable, and control of microbial contamination are only essential when stipulated by the requirements of the drug product process. They do however offer an engineering solution to the risk of cross-contamination. For additional guidance see HVAC section of "ISPE Baseline Guide: Active Pharmaceutical Ingredients" Second Edition June 2007, "ISPE Good Practice Guide: Heating, Ventilating & Air Conditioning (HVAC)" September 2009 and its supplement "ISPE HVAC and Process Equipment Air Filters" December 2019.

The key requirement is that building controls and procedures are in place to avoid contamination at any of the steps after purification of the API.

The "ISPE Baseline Guide: Active Pharmaceutical Ingredients" Second Edition June 2007 offers detailed guidance on how to assess the risk of contamination and defines the options for engineering solutions appropriate to the risk.

Chapter 9 Packaging and Identification Labelling of APIs and Intermediates

9.1 General

The focus of this chapter is mainly on packaging and labelling operations of API's and intermediates intended for shipment to third parties and it is not the intention that all requirements have to be met for internal transport at one site under the manufacturers' control.

9.10	<u>Labelling materials</u> : Applicable only for pre-printed labels or labels that are pre-printed or printed by on site computer and stored. For labels which are printed on demand, written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing and release, and handling of blank labels - bearing no information at all - are not applicable. (A label is only considered as a label if product or batch related information is imprinted).
9.11	See remarks 9.10
9.12	See remarks 9.10

9.2 Packaging Materials

Appropriate packaging materials to be used should be defined in the master production instruction (see chapter 6.41 for reference). For APIs and, when appropriate, for commercially available intermediates the suitability of packaging materials should be supported by product stability testing.

9.20	<p>Most APIs are stored and shipped in fibre or PE drum as secondary/tertiary packaging with polyethylene liners or polyethylene bags as primary packaging. The inner lining or bag in direct contact with the API should be at least of food grade plastic. If other material is used as a primary container the compatibility with the product must be ensured.</p> <p>. The inner packaging should be controlled by the company with respect to identity and traceability.</p> <p>Suppliers of packaging material should be part of the supplier qualification program.</p>
9.21	<p>Industry practice is to inspect these packaging materials for defects and cleanliness. Sanitising containers and/or sterilizing containers is only applicable for API packaging materials used in sterile and aseptic sterile API manufacturing.</p> <p>The presence of potential extractable's and leachable's should be known and risk based assessed. (Except for additives listed by EU Pharmacopeia)</p>
9.22	<ul style="list-style-type: none"> • <u>For the same product</u>: Visual inspection should be enough, effectiveness of cleaning should have been demonstrated (e.g. by cleaning validation). • <u>For multi-use</u>: Cleaning procedure has to be validated, or at a minimum, depending on the stage of manufacture, analytical verification has to be performed. <p><u>Remarks</u>: Validation is only applicable if product is in direct contact with the surface of the container, and not if in-liners are used (PE bags etc.)</p>

9.3	For the API industry, on site computer printed labels are the norm. Pre-printed labels are exceptions. Most of the ICH statements addressed pre-printed labels. Computer printed labels are typically printed “on demand” basis and little or no storage is needed.
9.30	Applicable only for pre-printed labels or labels that are printed by on site computer and stored. For labels printed “on demand” blank roles of label are not applicable. See 9.10
9.31	The main focus is on pre-printed labels or labels that are printed by on site computer and stored. For labels printed on demand also procedures should be in place to check “number of labels demanded”, “number of labels printed”, number of labels put on the drums”, “number of labels attached to the batch record or other traceable documents, e.g. shipping / dispensing documents”, “number of labels destroyed”. These actions should be documented and traceable Additionally, a check that the label(s) conform to the master should be documented in the batch record or other dispensing records. (See also chapter 6.52 for reference). Discrepancies referred to should be treated as critical deviations and thus the results of the investigation should be approved by the Quality Unit and include measures to be taken to prevent reoccurrence.
9.32	See comments 9.31, returned labels are not likely to occur if “on demand” printed labels are used. If too much labels have been demanded, they should be destroyed and this activity should be documented in the batch record.
9.33	–
9.34	Programmable printing devices used to print labels on demand should not be subject to validation. Printing devices may be controlled by a template, which may be changed by designated personnel according to an established procedure(s). Should also fall under the change control procedure.
9.35	The examination of printed labels regarding proper identity and conformity with a master should be documented in the batch record or other documentation systems in place, e.g. dispensing records. (see 9.44, examination and documentation of packaging and labelling).
9.36	See 9.31 for reference.

9.4 Packaging and Labelling Operations

9.40	Additionally, to primary packaging and labelling after completion of production labelling with customer and/or country specific information is common practice. These activities have to be fully documented on paper or in an electronic system (e.g. in the batch record or dispensing records)
9.41	Before starting labelling, operations refer to ICH Q7 clause 9.44. Only one batch can be labelled at the same time in the same area. Also barcode systems correlating batches to labels could be used to prevent mix-ups. This procedure applies to both internal and expedition process.
9.42	–

9.43	<p>In case label changes are required this need to be supported by change control Special attention should be given in case the retest date or storage/shipping conditions are modified and mentioned on the label. This process should be described in a procedure. Included but not limited to:</p> <ul style="list-style-type: none">- Update master data accordingly (paper based or electronic)- Control of the status of existing stock to avoid inappropriate use- For existing stock, process to update labels and/or issue new labels, manually or electronic- Documentation of activities (example: check-list, Form, in change control)
9.44	<p>A line clearance instruction should be in place (e.g. Batch record, cleaning record, procedure, ...)</p>
9.45	<p>Examination results should be documented but not necessarily in the batch record. The documentation could be attached to the batch record. Also, other systems which are retrievable could be used. Applicable practices as stated above for relabelling should be considered</p>
9.46	<p>It is recommended that company specific seals should be used particularly as imported material are often opened by customs and it should be apparent that such opening and re-sealing has taken place.</p>

Chapter 10 Storage and Distribution

10.1 Warehousing procedures

This chapter covers the storage of all materials. In general, all storage conditions should be established based on stability data or suitability for use information. This data can be derived from formal stability studies for APIs. For intermediates and other materials, they might be obtained from scientific considerations, product history, and published data or from reanalysis of materials stored for some time. Controlled storage conditions only apply for materials where stability studies have demonstrated that specific storage conditions are required regarding temperature effects and/ or pick-up of moisture in the standard packaging.

Advice on storage conditions (specific and unspecific) is given in USP “General Notices, Storage Temperature and Humidity” where also the concept of applying the mean kinetic temperature approach is explained. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations. (See also ICH Q1a for reference).

It is not always necessary to have evidence of on-going storage conditions. It is a current expectation from the health authorities to have at least storage condition monitoring systems in place in the final API storage area when the stored material could be negatively affected by excessive temperatures or humidity over a longer period of time. Periodic review of the monitoring is expected.

Besides being indicated by stability studies other reasons can result in the need for special storage conditions. Examples could be: avoidance of odorous or highly toxic materials in the proximity of the API, narcotic materials segregation,...

10.10 For API's **not** requiring specific storage conditions, ambient storage with no specific controls over temperature or humidity is accepted. However, temperature and/or humidity monitoring to support appropriate storage of API's in compliance with stability data is required.

In cases where storage conditions are critical, monitoring control devices should be appropriately calibrated, and it may be necessary to qualify the warehouse itself with respect to temperature and humidity distribution. (for reference, see chapter 12.3 “Qualification”). Depending on local temperature and humidity differences between seasons, the impact of seasonal changes might increase the warehouse temperature and humidity mapping effort.

The location of any temperature and humidity measuring devices should be justified and based on the worst-case locations. References on how to perform mapping can be found on:

- 1 – USP<1079> and <659>;
- 2 - Guide IEC 60068 – Environmental Testing - part 1 to 7.
- 3 – Guide to Good Distribution Practices of Medicinal Products for Human Use, March 2021 from HPRA
- 4 - Guideline on principles of Good Distribution Practice of Active Substances for Medicinal products for human use (2015/C 95/01)
- 5- WHO: Temperature mapping of storage areas, technical supplement to WHO technical reports series No 961, 2011 from May 2015.

	<p>Acceptance criteria for different storage conditions (examples are: controlled room temperature, cold chain, freezers, ...) can be found in the GDPs, EMA directive 2001/83/EC and in the HPRA Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances with reference IA-G0011-3 from October 2020. The calculation and use of mean kinetic temperature is included.</p> <p>If special storage conditions are required it should be mentioned on the label as specified in CPMP/QWP/609/96/Rev 2-part B declaration of storage conditions for active substances.</p>
10.11	<p>Acceptable separate storage areas for such activities may solely be marked shelving or floor spaces with the exception of areas for rejected, returned or recalled products in which physical barriers should be utilised to prevent unauthorised use, e.g. locked areas or rooms.</p> <p>Alternative systems may be validated computerised stock control with restricted access. When using these systems the use of separated areas is not required, however the preference for using physical barriers is still common. Therefore, equivalent control should be demonstrated.</p> <p>For intermediates the storage conditions can be based on product knowledge, development data and/or stability studies. Justification should be documented. For purchased Raw Materials the manufacturer advised storage conditions should be applied unless otherwise justified.</p>

10.2 Distribution procedures

	<p>The focus of this chapter is on shipping of APIs and commercial available intermediates to third parties and not on internal transport and/or transport between different sites of the same company. Irrespective if a shipment is performed within a company or to third parties adequate supply chain controls should be in place.</p> <p>For API shipments, a system should be in place to assure packaging and supply chain integrity. If needed, special controls should be in place to assure shipments meet the defined requirements. Examples are: unique seals, temp tales, defined R&R of changes in product ownership during the shipment and supply chain.</p> <p>For shipments between different sites of the same company a documented risk based approach can be used to justify not applying these standards.</p>
10.20	<p>The process of transfer under quarantine should be proceduralised.</p> <p>Quality Unit of both sites need to approve the shipment under quarantine and the receiving site cannot use the material before a CoA of the batch in scope is issued. Before shipment under quarantine the manufacturing batch record should be reviewed and approved by the Quality Unit.</p> <p>For subcontracted activities, the formal quality agreement should cover this scenario as recommended in Chapter 16 and APIC guideline: https://apic.cefic.org/pub/APICQAGuidelinecomplete_new_final2.0_20171102_clean ed.pdf</p>

	<p>When the finished product manufacturer request the transfer under quarantine because of the circumstances of the API, such process should be established in a written agreement between the finished product manufacturer and the API manufacturer.</p> <p>For more details see ICHQ7 Q&A Chapter 10, Storage and Distribution 1st question</p>
10.21	<p>Logistics companies who are contracted to move API should be qualified. A quality agreement (or equivalent) should also be in place which details the key requirements for the safe and effective transportation of the API. Appropriate protective outer packaging and a suitable transportation should be chosen to avoid damage during transport. For sensitive products, special shipping conditions should also be specified. Records of those conditions should be available to the manufacture on demand and at any time.</p> <p>The shipping conditions records should be reviewed for compliance to the acceptance criteria on arrival. If deviations occurred an investigation should be initiated and actions justified and documented.</p>
10.22	<p>Only applicable if safety or API / commercial intermediate stability (indicated by stability data) require special conditions and / or instructions. For stable and / or harmless APIs normally no specific storage conditions are required on the label. Independently from GMPs, national and international laws and regulations have to be followed.</p>
10.23	<p>Appropriate transport and storage requirements are typically conveyed with the logistic company on the bill of lading. If special storage conditions are required to avoid alteration, it might be necessary to monitor the shipping conditions and to evaluate any trend and records of these conditions should be retained.</p>
10.24	<p>Full traceability for all shipments from the manufacturer to its external customer(s) has to be in place.</p> <p>If APIs or intermediates are delivered to a broker, full traceability has to be ensured by the broker as well according to chapter 17. (Remarks: In this case the final user of the API is unknown to the API producer, therefore full traceability to the end customer is the responsibility of the broker).</p>

Chapter 11 Laboratory Controls

11.1 General Control

11.10	<p>The laboratory facilities at disposal of the Quality Unit can be internal or external e.g.:</p> <ul style="list-style-type: none"> In the Quality Control Department In the Production Department At other sites of the same organisation (e.g. company which operates to the same quality procedures) As contract laboratories, provided they comply with Chapter 16. <p>Whatever the laboratory selected, the responsibilities remain within the Quality Unit of the manufacturer (see 2.22).</p> <p>Design and construction of the facilities (internal or external) have to be in accordance with the type of tests performed (i.e. microbiological tests require sample protection from particulate contamination when handled, the weighing room should not have</p>
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	vibration, ...). Separate rooms for different kind of tests (microbiology, chemistry, powder handling, etc.) can be needed.
11.11	<p>There should be SOPs (approved by the Quality Unit) describing:</p> <ul style="list-style-type: none"> • <u>Sampling</u> Different approaches are possible: a general method, different methods grouping products (liquids, solids, dangerous, hygroscopic, ...), one sampling SOP for each product, or a combination of them. Clearly defined and documented procedures have to be available. They should take into account requirements of 7.33. Sampling plans for raw materials, intermediates and APIs have to be available, and scientifically justified. • <u>Testing</u> - Analytical methods and test procedures should be cross referenced (e.g. pharmacopoeia). The procedures should have adequate, clear and sufficient detail on how to perform the tests. Clear calculations are needed to allow the results to be generated and accurately assessed against specifications. Electronic systems used to perform the analytical calculations should be validated and controlled to ensure data integrity is maintained. <p>An SOP should be in place to define the rounding rules as described in the pharmacopoeia, how they apply to the calculations and how to assess the result versus the specification criteria.</p> <p>If analytical results need to be averaged to obtain the final value, the process used for averaging should be described in a SOP.</p> <p>Control charts can be used in detecting trends and atypical results which may require additional evaluation. Care should be taken when averaging results involving atypical values (e.g. outliers) or when single values are out of the specification limit. Reference: FDA guidance for industry investigation of (OOS) test results for pharmaceutical production (October 2006 – chapter IV.C reporting testing results).</p> <ul style="list-style-type: none"> • <u>Approval/rejection of materials</u> <u>An SOP should be in place to define the responsibilities within the organization (e.g. Quality Unit, ...) related with the approval / rejection of the different type of materials (e.g. incoming materials, final API).</u> • <u>Recording and storage of laboratory data</u> The content of the SOP(s) has to be in accordance with requirements of 6.6, and should describe what data should be recorded and reported, and where and how long this data should be retained. The responsibility for the integrity of retained records and relevant raw data should be assigned. See 6.13 when establishing retention times. When managing electronic data, systems should be appropriately validated (see the current GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture for reference). The integrity and retrievability of the data should be guaranteed throughout the retention period.

11.12	Chapter 11.12 is self-explaining.
11.13	<p>When establishing API specifications</p> <p>A) relevant ICH guidelines/documents should be taken into account: examples are: ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. ICH Q6B: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological / Biological products ICH Q3A: Impurities Testing Guideline: Impurities in New Drug Substances. ICH Q3C: Impurities: Residual Solvents ICH M7: assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. ICH Q3D: guideline for elemental impurities</p> <p>B) And/or the specifications can be based on the design space using design of experiments when available.</p>
11.14	<p>In order to demonstrate test results are documented at the time of execution the laboratory can use laboratory notebooks (bound notebook pre-numbered) or use controlled pre-numbered analytical forms. An electronic and validated data collection system can also be used to record the raw data at the time it is generated.</p> <p>Departures from the procedures should be managed according to the deviation SOP.</p>
11.15	<p>Both documents below give good guidance on how to perform an OOS investigation/ - FDA guidance for industry investigation of (OOS) test results for pharmaceutical production (October 2006)</p> <p>-MHRA: https://mhrainspectorate.blog.gov.uk/2018/03/02/out-of-specification-guidance/</p> <p>OOT results should be investigated and documented.</p> <p>Impact on other analyses/tests (results)/batches/products, should be considered as part of the OOS/OOT investigation (see 6.53).</p>
11.16	<p>“Use by” dates are appropriate for those analytical reagents and standard solutions where its purity or standardised value can potentially change with the time.</p> <p>If the supplier provides a “use by” this should be applied.</p> <p>If no “use by” is available the company should establish the maximum “use by” time based on scientific justification. This (“use by” and opening date) should be reflected on the label and specified in a SOP.</p> <p>When appropriate, standard solutions can be re-standardised and a new “use by” date can be assigned and documented.</p>
11.17	<p>A SOP describing the policy of the company related to standards certification (both primary and secondary) use, records, obtaining, identification, maximum use time or recertification time if applicable and storage requirements should be in place.</p> <p>When methods described in an official pharmacopoeia require reference standards, they have to be acquired from the relevant pharmacopoeia.</p> <p>The routine use of a secondary standard tested against the primary standard is an acceptable practice if adequately certified (USP general notices).</p> <p>The level of characterization of the standard is based on the intended use of the standard: examples are:</p> <p>- identification marker, purity, potency, ...</p> <p>If reference standards are certified by the user relevant analytical methods should be</p>

	<p>used to assure the correct identification/ potency/purity as applicable of the standard defined.</p> <p>Analytical methods and techniques additional to the release specification can be used to characterize the standard.</p> <p>Re-certification of standards is allowed for material beyond its original retest date as long as it meets the criteria for its intended use. (example: content within specification if used for HPLC assay).</p>
11.18	<p>For non compendial APIs, in house standards or those obtained from other sources may be used. Accepting a standard may require different tests than those applied to the regular product in order to confirm its suitability (purity determination by absolute methods, not applied currently in process testing), however some routine tests may be omitted. When a standard is used as a reference point for assays the mean and standard deviation of the assigned assay value should be known.</p> <p>The method for obtaining and testing an in house primary standard should be described in writing. The purity may be assigned through a specific test for purity or by assigning a purity of 100 % taking away all the impurities (including water) determined by validated methods.</p> <p>Records of the tests carried out to identify and determine the purity should be maintained.</p> <p>A retest/expiration date should be assigned to the standard. It may need to be re-qualified.</p> <p>A formal certification of standards is needed when these are sent outside the control of the manufacturer.</p>
11.19	<p>The method of obtaining and testing secondary standards should be described in writing and the outcome of the testing should be summarized in a certificate of analysis or similar document.</p> <p>The purity of those should be known. If used in assay determination the purity should be assigned testing it against the primary standard. Traceability to the original primary standard should be documented.</p> <p>A retest/expiration date should be assigned.</p> <p>Storage and inventory practices for the standards should be the same as the practices for APIs (e.g. controlled access, storage conditions, inventory control, ...).</p>

11.2 Testing of Intermediates and APIs

11.20	Appropriate laboratory tests mean tests designed to support the overall control strategy for the API and/or intermediate(s).
11.21	Guidance for defining impurity profile(s) is provided in ICH Q3A, Q3C, Q3D and M7.
11.22	<p>The intent of this section is to pro-actively ensure trends/changes in impurity profile are identified and acted upon accordingly.</p> <p>The frequency of review of the purity profile versus historical batches can be based on:</p> <ul style="list-style-type: none"> - campaign length - number of batches produced over a period of time - Analyses of statistical process data

	<ul style="list-style-type: none"> - Trend analyses of analytical data - Using continuous process verification <p>This should be documented in writing and approved by the quality unit. However, it should be performed at a minimum on annual basis as part of the annual product review.</p>
11.23	See and follow ICH Q6A and ICH Q6B to determine if a defined microbial quality/specification is necessary.

11.3 Validation of Analytical Procedures

see Section 12.

11.4 Certificates of Analysis

11.40	<p>Authentic: true, accurate record of results obtained, signed (also electronically) by authorised person from Quality Unit and dated for every batch (API and/or Intermediate).</p> <p>A certificate of analysis should be issued when material is shipped outside the control of the manufacturer.</p>
11.41	<p>The Certificate of Analysis requires the date of manufacture (there must be a procedure that describes how the manufacturing date is defined. Preferably be set by the final purification step of the API).</p> <p>Retest and expiry dates are calculated from the manufacturing date.</p>
11.42	<p>Actual values should be reported if numerical results are obtained.</p> <p>If the result is lower than the limit of detection (LOD) the result is reported as “not detected” (ND).</p> <p>If the result is between the LOD and limit of Quantification (LOQ) the result is reported as < LOQ.</p> <p>Results above the LOQ must be reported with the actual numerical result.</p> <p>Non-numeric results can be reported as “Conforms or complies”.</p> <p>Certificates should make reference to the analytical test methods used. This can be done by referring each individual test ID on the CoA or by making a reference to the overall specification used.</p> <p>Certificates of Analysis for blended batches should be based on the results of sampling and testing the blend and not just taken from one of the components.</p>
11.43	<p>The signature can be a manual signature or produced by a validated computer system which provides a degree of control equivalent to a manual signature.</p> <p>The certificate of analysis should allow traceability to the original manufacturing site (source) and the way to contact the organisation that issues it.</p>
11.44	Chapter 11.44. is self-explained.

11.5 Stability Monitoring of APIs

11.50	Results of on-going stability program have to be evaluated at least in the product quality reviews.
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	<p>The evaluation should include trending of the stability data.</p> <p>Batches should be included in the stability testing program within one month after its manufacturing date. For batches that are placed under stability later than one month after its manufacturing date an additional time point should be added to the stability protocol that corresponds to the retest/expiry date of the product.</p> <p>The following documents may be used as guidance:</p> <ul style="list-style-type: none"> - ICH Q1A: Stability Testing Guidelines: Stability Testing of New Drug Substances and Products. - ICH Q1B: Photo stability Testing of New Active Substances and medicinal Products. - ICH Q1E: Evaluation for Stability Data - CPMP/QWP/122/02 Rev.1 corr: Guideline on Stability testing: Stability testing of existing active substances and related finished products. - EMA/CHMP/CVMP/QWP/441071/2011-Rev.2 guideline on stability testing for applications for variations to a marketing authorisation. <p>For intermediates, shipped outside the company control data should be available to support the required storage period and distribution conditions.</p> <p>For intermediates stored on site data should be available if necessary to support the defined retest period.</p>
11.51	<p>Follow the requirements of Section 12.8 for validation of test procedures used in stability testing.</p> <p>To demonstrate that a method is stability indicating usually stress conditions are applied to the API (temperature, humidity, pH, Oxygen, light ...) in order to achieve a significant degradation and determination of the purity and impurities.</p> <p>Setting up a mass balance can help justifying the selection of method(s).</p>
11.52	<p>Ideally there is a stability sample for each pulling point stored in a miniaturised container equal to the commercial package.</p> <p>In case of technical constrains, storage of different individual bags in the same primary package for each pulling point of the API in the same small-scale secondary package is acceptable.</p> <p>To store multiple pulling samples inside an additional package is not simulating the market container.</p>
11.53	<p>First 3 commercial production batches should normally be placed on the stability program. However, an example where less than 3 batches can be applied is when the commercial batches are produced in equivalent equipment using the same process as that previously used in development.</p>
11.54	<p>The batch put on stability monitoring should be representative for routine production.</p> <p>When stability of API is beyond two years the annual batch only needs to be tested at 0, 12, 24, 36... months.</p> <p>Based on scientific judgement, major changes or critical deviations may be required for additional batches to be placed on stability and / or more frequent testing.</p> <p>Annual stability monitoring should also consider reprocessed batches – for each type of reprocessing the batch should enter the annual surveillance programme.</p>

	For subsequent reprocessing of the same type an evaluation must be made for the need to put the batch in the annual surveillance programme.
11.55	Chapter 11.55 is self-explained.
11.56	For intermediates the stability storage conditions may be defined using data that is not generated according to the ICH guidelines on stability.

11.6 Expiry and Retest Dating

11.60	<p>The supporting stability information on intermediates is not necessary to be obtained through stability studies complying with the ICH requirements for APIs. It may also be obtained from published data or from studies based on test results of materials. (e.g. Stored under normal warehouse conditions).</p> <p>The test method(s) used should be suitable to support stability storage conditions. Test methods other than those used for the release may be considered.</p>
11.61	<p>The use of a retest date is recommended, this will allow using the API after this date, provided it complies with the specifications. See definition of Retest date.</p> <p>Based on the ICH Q7 Q&A document it is allowed to extend the API retest date based on:</p> <ul style="list-style-type: none"> - 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. <p>Multiple retesting to extend the API retest date of a specific batch is acceptable.</p> <p>The time between testing and use should be limited and justified.</p> <p>Material with an expiry date assigned cannot be retested to extend the shelf life.</p>
11.62	<p>To carry out stability tests following ICH guidelines on pilot scale batches is recommended, the data obtained (provided that commercial manufacturing scale employs the same manufacturing method and procedures and the quality of the API is equivalent) may be used to establish a preliminary retest period. When stability data from first commercial manufacturing batches are being obtained, this preliminary retest period can be extended if they allow it. Content of 11.52 also applies.</p>
11.63	<p>Retention samples should not be used.</p> <p>When performing a retest with the purpose to extend the use of the batch, the sample should be taken from the containers of the actual batch at the location where the API is stored. The sample should be representative for all the remainder of the batch under the control of the manufacturer. When containers from the same batch are stored at different locations/regions, outside the control of the original manufacturer representative sample from each location should be retested, when required.</p>

11.7 Reserve/Retention Samples

11.70	<p>Reserve samples should be representative of the batch and prepared from the same composite sample than the sample used for release testing.</p> <p>The storage area for reserve/retention samples should be monitored for temperature and if applicable, also for humidity.</p> <p>The storage conditions should be equal or better than the label storage conditions.</p>
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11.71	<p>To avoid having different retention times for reserve samples for each product and each batch manufactured, it may be workable for companies to define a unique retention time for all batches and products of 3 years after the expiry or retest date (provided that any batch or a part of the batch is not distributed after its retest date).</p> <p>The retention times are a minimum and provided these are met, reserve samples may be disposed of later than the minimum times (e.g. in order to also cover the shelf life of the finished drug product made from this API).</p>
11.72	Chapter 11.72 is self-explained

Chapter 12 Validation

12.1 Validation Policy

12.10	<p>Overall Policy</p> <p>The company should document clear and unambiguous policy related to all validation activities. Qualification activities are considered to be an integral part of validation. The policy should clearly show a company's rationale towards validation and detail how it will approach each key activity.</p> <p>Responsibilities and roles should be clearly defined and documented to ensure that commitment is made at the appropriate level.</p> <p>The policy should reflect the expectations of the Health Authorities validation guidelines.</p>
12.11	<p>Critical Parameters/Attributes</p> <p>General considerations:</p> <p>A Critical Process Parameter (CPP) is a parameter in the full process (from introduction of the starting material to the final API) that has an impact on a critical quality attribute of the final API.</p> <p>“A Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality” (Quoted from ICH Q11)</p> <p>“Continuous Process Verification (CPV) is an alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated” (Quoted from ICH Q11)</p> <p>CPV requires trending of CPPs and CQAs. The decision, which CPPs and CQAs should be trended, may be based on a risk assessment.</p> <p>To assure non-critical process steps are manufactured within the pre-defined specifications of that particular step “key process parameters” (parameters that may impact yield, cause process difficulties,...) can be defined to assure compliance to the individual specs.</p>

	<p>A criticality assessment should be performed to map out CPPs prior to validation (for example ICH Q9 and Q11). These parameters need careful consideration as they will form the basis for assessing the system to be validated.</p> <p>Ranges used for each critical parameter should be well defined and supported by development data and/or historical data. These parameters, if not adequately controlled, could affect the critical quality attributes of the API.</p> <p>Further details on critical parameters can be found for example in:</p> <ul style="list-style-type: none"> - ICH Q11 (Development and manufacture of drug substances) - FDA guideline (FDA Guidance for Industry – Process Validation: General Principles and Practices) - only as a reference EMA process validation guideline (Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 15: Qualification and Validation)
12.12	<p>Validation should extend to those operations deemed to be critical.</p> <p>Protocols used in validation (process, analytical, equipment, facilities, IT, utilities...) should encompass those operations deemed to be critical. Non-critical operations do not need to form part of the validation study.</p> <p>Once validated, CPV may be applied. Any changes need to follow change control procedures to evaluate the impact on the current validation status of the operation.</p>

12.2 Validation Documentation

12.20	<p>Review and Approval</p> <p>Review and approval of protocols prior to the initiation of validation activities needs to come not only from the QU but also from personnel who are competent and have the authority to support the validation.</p> <p>Roles and responsibilities should be clearly described to assure commitment is made at appropriate departmental level.</p>
12.21	<p>Acceptance Criteria</p> <p>The validation protocol should refer to completion of unit operations qualification and analytical methods validation before initiation of the process validation.</p> <p>EMA and FDA require that the rationale for defining the number of validation runs should be scientifically justified and documented.</p> <p>The protocol must specify all critical parameters. For example, process validation levels of impurities need to be controlled in line with any registered specification. Meeting the limits for these impurities consistently would be a key acceptance criterion.</p> <p>Acceptance criteria are defined in validation protocols in order to assure robustness and consistency of the manufacturing process.</p> <p>Depending on the critical process steps extra validation activities may be needed, examples are: homogeneity, drying profile, quality of individual centrifuge loads....</p> <p>The validation protocol should specify the batch release strategy and the need to include the batch(s) in the stability program.</p>

12.22	<p>Deviations Observed</p> <p>All deviations related to the validation exercise should be documented and for critical deviations a more detailed explanation is expected in the validation report. Conclusions of the impact of the deviation on the validation exercise and corrective actions need to be documented.</p> <p>When the acceptance criteria are not met, the validation should be evaluated as to whether it is best to stop the validation or amend the protocol to manufacture additional batches. Careful consideration is required before this decision is made as the underlying reason for the failure should be fully understood and acted on. Equipment failure, low yield... that are not process related may allow to extend the validation exercise to complete the process validation.</p>
12.23	<p>The validation report should reflect the explanation for the departure(s). The protocol does not necessarily need to be amended. Traceability should be assured</p>

12.3 Qualification

12.30	<p>For full comment on Qualification see ISPE Baseline Guide on " Commissioning and Qualification".</p> <ul style="list-style-type: none"> • Design Qualification is documented evidence that: <ul style="list-style-type: none"> – User Requirements document has been established by production, engineering and/or technical/maintenance services. – Technical propositions made by engineering department have been approved by concerned units as production, technical/maintenance services, quality control, quality assurance units in terms of equipment design and automatic operation design. – A multidisciplinary team composes an equipment risk assessment - Documented evidence can consist in formal approval of: <ul style="list-style-type: none"> • Meeting minutes • Facility layouts • PID • Supplier detailed layout • Design Qualification should apply to (in terms of equipment and/or automatic operation): <ul style="list-style-type: none"> – new process – new step in actual process – modification of an equipment in a process • Installation Qualification: the output of the IQ exercise should be a PI&D as built • Operational Qualification can be performed in 2 phases OQ part 1: element by element OQ part 2: as a whole installation (example water/solvent batch) • Performance Qualification can be considered at the OQ part 2 or as part of the Process Validation.
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12.4 Approaches to Process Validation

12.40	<p>Process Validation</p> <p>The purpose of process validation is to demonstrate that a particular process can perform effectively in a robust and consistent manner to produce material that meets predetermined specifications and quality attributes.</p> <p>Critical process steps should be validated, steps identified in the criticality assessment as non-critical process steps could be validated to a justified lower extent (for example, less number of batches, drying profile, quality of individual centrifuge loads ,...).</p>
12.41	---
12.42	<p>Prospective validation can be performed:</p> <ul style="list-style-type: none"> - Traditional way (3 consecutive successful batches). EMA and FDA require that the rationale for defining the number of validation runs should be scientifically justified and documented (EMA is expecting at least 3 validation batches). - Enhanced way based on quality by design using design of experiments and continuous quality improvement <p>As part of the Continued Process Verification life cycle approach</p>
12.43	<p>Concurrent validation</p> <p>An explanation should be provided why a concurrent validation is performed instead of a prospective validation. Concurrent validation is a particular form of prospective validation, in which the batch or batches produced are released, based the pre-defined acceptance criteria in the protocol, before the entire validation study is complete.</p>
12.44	–
12.45	<p>Retrospective Validation</p> <p>APIC advises to perform a prospective approach for such situations taken into account previous batches through statistical evaluation.</p> <p>Retrospective validation is only accepted under the circumstances defined in ICH Q7 Q&A document (see Chapter 21).</p> <p>Retrospective validation requires a protocol that covers in detail the acceptance criteria and batch information that will form the basis for validation.</p> <p>Batches that fail to meet specification or are out of trend need to be discussed.</p> <p>The number of batches chosen should be statistically based. The "general rule" from the above judgement is that between 20-30 batches is required, but a firm can depart from this number provided it can support any such departure with statistical or other evidence that supports validation.</p> <p>APIC advises not to use retain samples as they are needed for potential complaint support and critical quality defect investigations.</p> <p>Use of retention samples (remaining from QC testing) for this purpose is the preferred option.</p>

12.5 Process Validation Program

12.50	The described 3 consecutive successful batches should be considered as a guide, important is to pre-define the number of batches involved in the validation exercise EMA and FDA require that the rationale for defining the number of validation runs should be scientifically justified and documented (EMA is expecting at least 3 validation batches).
12.51	–
12.52	The process validation report should not refer to comparability of the impurity profile alone but all critical quality attributes of the API should be in specification and be comparable or better than the reference batches The rationale for selecting reference batches must be justified

12.6 Periodic Review of Validated Systems

12.60	<p>Revalidation</p> <p>Product Quality Reviews (PQR) (see 2.5) should assess the requirement for revalidation as part of the Continuous Process Verification program.</p> <p>Significant changes made to systems/processes or significant changes in product quality (see chapter 13) will require evaluation for revalidation.</p> <p>Besides the PQR a periodical System Quality Review (SQR) should be in place for systems like utilities, equipment, IT-systems. The frequency to perform these SQR's is depending to the criticality of the system in the API manufacturing process and must be pre-defined.</p>
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12.7 Cleaning Validation

12.70 – 12.76	<p>See APIC guide on cleaning validation for full comment:</p> <p>“Guidance on aspects of cleaning validation in Active Pharmaceutical Ingredient plants”</p> <p>Building up validation data, the use of equipment for further manufacturing should be based on cleaning verification data.</p> <p>Three successful applications are generally accepted to consider the dirty hold time (DHT) as validated. Another number could be considered if based on a risk assessment.</p> <p>The rationale to perform clean hold time (CHT) validation must be specified and based on a risk assessment.</p> <p>Validation of CHT is usually restricted to equipment used in final stages of API manufacturing and for final API having micro release specifications.</p> <p>This risk assessment should include the type and use of the product and the equipment storage conditions</p> <p>Three successful applications are generally accepted to consider the (CHT) as validated. Another number could be considered if based on a risk assessment.</p>
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	<p>Several approaches can be followed for the CHT and DHT cleaning validation such as bracketing, per type of equipment, worst case principle but always based on data. The approach chosen should always be described in a protocol where and how sampling, acceptance criteria, validate analytical methods is defined.</p> <p>Every time a new product is introduced the cleaning validation including CHT and DHT and validated status should be introduced and assessed part of the relevant quality management system for cleaning validation</p> <p>Continuous verification of the cleaning validation status should be applied.</p> <p>A system should be in place to assure that exceeding CHT and/or DHT is captured and actions defined before using the equipment. Risk assessment can be applied.</p>
12.72	<p>Besides cleaning agents “materials” should also be read as equipment contact materials. Depending on the type of product contact material (e.g.: glass lined, Stainless steel, PVC....) cleaning validation must be performed on each type of equipment material as applicable.</p>

12.8 Validation of Analytical Methods

12.80	<p>Analytical methods used directly from recognised standard references (e.g. Pharmacopoeia) need only to be demonstrated suitable for use. System suitability tests can be found in European Pharmacopoeia.</p> <p>If modified pharmacopoeia methods or in-house methods (non-pharmacopoeia) are applied for compendia APIs equivalence with the relevant pharmacopoeia the method has to be demonstrated and a report has to be made available. Regulatory impact need to be considered prior to implementation.</p>
12.81	<p>Guidance on the levels of analytical method validation can be found in ICH Q2.</p> <p>Minimum analytical validation requirements related to the type of test can be found in USP General Chapter <1225> validation of compendial procedures.</p> <p>APIC advises to perform analytical method validation for Starting Materials and critical raw materials.</p> <p>For non-critical raw materials and non-critical intermediates, the level of validation should be based on a risk assessment and related to its intended use.</p> <p>The level of the validation required for in-process controls should be evaluated depending on the influence on the final API quality.</p>
12.82	<p>Appropriate qualification</p> <p>Qualification can be performed in house or provided by the equipment supplier or qualified contractor.</p> <p>If supplier qualification information is used it should be approved by the Quality Unit of the API manufacturer as suitable for its intended use.</p> <p>If the supplier is used as a contractor, they should be handled in accordance to the requirements specified in Chapter 16.</p> <p>Qualification of contract labs is described in the APIC document “Guideline for qualification & management of contract Quality Control laboratories”.</p>
12.83	<p>Modification needs to be covered by a change control system.</p>

Chapter 13 Change Control

13.10	Compliance to Regulatory filings should be assessed as well as GMP implications with the change control system
13.11	<p>Having defined the quality of an intermediate or API, usually in terms of a specification and/or CQA, it is essential to maintain this quality, as there is interrelationship between "quality" and the two other essential properties of an API, "safety and efficacy", ANY change which may affect the quality of the intermediate or API may also change the safety and efficacy. It is thus essential that all changes are evaluated before being introduced.</p> <p>It is intended that not only changes to the way of producing or analysing the product should be covered by the Change Control System, (CCS), but this should also cover other changes to for examples buildings and equipment, utilities, suppliers of starting materials and critical raw Materials, etc.</p> <p>Changes in any part of the quality system should not be confused with "deviations" and the ICH EWG made it clear that the procedure for dealing with deviation, (as described in § 2.17 and § 8.15 as well as §.6.72) is not the same as that to be used for changes. The diagrams below makes the difference between "a change" and "a deviation" apparent. A planned "deviation" does not exist! It should be handled as a Change</p> <div style="text-align: center;"> <p>NOT PLANNED <u>==</u> DEVIATION <u>was not planned</u> and now has already occurred</p> <p> ↑ EVENT ↓</p> <p>PLANNED <u>==</u> CHANGE <u>is planned to occur</u> i.e. the event has not occurred yet; but there is however the intention to <u>do something different in the future.</u></p> </div> <p>A change can be temporary or permanent. Temporary change control can be used for limited time, but also for trial (example: specific number of batches with the possibility to change it to permanent) As preparation for a possible Change TRIALS are often initiated. TRIAL is defined as something that is planned for a limited time.</p>

However as “Trials” are not mentioned anywhere in the ICH Guide, it will be advisable to handle them under the CCS however the approval process to conduct a "Trial" should be very simple. Precautions should be taken to prevent "Trial material" leaving the premises, or other being used without authorisation. It is recommended to include the description of the trial procedure in the CCS SOP.

The word “formal” indicates that the way in which the CCS needs to be laid down in writing and approved by appropriate persons including (according to § 2.22 – 6) someone from the quality unit.

It would be acceptable to have more than one CCS in a company and there might be several “formal” CCSs covering marketing-relevant changes, quality-relevant changes, engineering changes, process changes etc. The essential element is however that the proposed changes are written, evaluated and approved.

ALL changes should be evaluated before being initiated. Thus, it is incorrect only to deal with changes that definitely will have an effect using the CCS.

Although theoretical only changes which could affect “productions and control” need to be handled under the CCS, nevertheless the ICH EWG intended that any changes which affect the “manufacture” (i.e. not only production and control, but also packaging, labelling and storage etc) should be handled by the CCS.

Like for like changes do not need change control however, case by case, change control might be applied to assure all necessary actions (example: an ID change of a measuring device in production, qualification work etc.) are executed timely.

If change control is not applied for a like for like change this change needs to be recorded as appropriate.

The definition for “like for like” needs to be clearly defined, justified and approved.

13.12 There are four key words which should govern how the CCS is run: Propose, Review, Evaluate and Approve. These are shown in the following flowsheet

<u>Activity in the Change Process</u>	<u>Relevant ICH Paragraph</u>
Possibly review of the proposed change with affected dosage form manufacturers and/or customers, where appropriate	§ 13.17
Propose a Change in writing	
↓	
Forward this Proposal to those units in the organisation who are best able to pass judgement by reviewing the implications on the proposal, one of which should be the responsible Quality Unit. (Other typical units could be the stability testing unit , development department, purchasing, production, costing, cleaning, safety etc). The Regulatory Affairs unit generally would also be asked to judge whether and where the change, if internally approved , might need external approval and/or requires customer notification. Usually the SOP governing Changes will specify within what time frame an answer should be given.	§ 13.12 § 13.13 § 13.16 § 1.1 (Last paragraph)
Have lists of the documents which will be affected by the Change prepared and compile an action plan with responsible persons to execute the actions	§ 13.14
↓	
Review and summarise the answers and prepare the Approval to proceed (or Rejection) statement , and have this signed.	§ 13.13
↓	
Request an evaluation of the success (or otherwise) of the change. This should be prepared by the originator of the original proposal and reviewed and approved by the Quality unit	§ 13.15

	<p>By using the word proposal, it is clear that an application, detailing what it is proposed to change, is necessary. It is recommended that this should not only cover the proposed change itself but should give some proof not only that the change will work (by having run “trials”), but also an indication of the cost of the change (i.e. the cost of generating new stability data). The fact that the words reviewed and approved are used twice indicates that the initial review and approval by the appropriate organisational unit needs to be followed by the review and approval by the QU(s) (a task assigned under § 2.22-9). This is particularly essential where the QU(s) may not have sufficient expertise to fully evaluate the implications of a proposed change, e.g. on the Marketing Approval, / DMF / API use. In a similar manner, it would be appropriate to review proposed changes to facilities, support systems (e.g. water treatment systems), or computers by persons with appropriate expertise who are independent of the person or group applying for the change. Some unit should draw up a list of customers who could be affected by the proposal. And inform the customers as required by the quality agreement.</p>
13.13	<p>The wording indicates that although a classification procedure may help such a classification procedure was not a requirement of a CCS.</p> <p>By using the words Scientific judgement, it is made clear that it is impossible in such a guide to prescribe exactly how each type of change should be dealt with. Thus, the justification for approving a proposed change should not slavishly follow a prescription, but each case should be judged on its merits.</p> <p>Although theoretically: there is no specific requirement to put the reasoning (justification) for approving (or rejecting) a proposed change in writing, companies are strongly advised to provide a written justification, (even if only in a few lines): This could for example include the reasoning why the proposed change is being approved, and why (or why not) a revalidation of the production process or analytical method is (or is not) necessary.</p>
13.14	<p>The text makes it clear that solely approving a change is insufficient, but there also needs to be a programme which identifies what needs to be done so that the approved change may be carried out. It is recommended to have a fixed template to assure all potential departments/processes are involved and evaluated.</p> <p>The critical words here are to ensure that documents affected by the changes are revised. The principle raised here is that of checking that the documents (e.g. DMF, other Regulatory documents, in-house instructions, and procedures, information given to customers, etc) which might be affected were actually revised. The EWG purposely gave no advice on how this should be done, and thus each company is free to devise its own procedure for meeting this requirement.</p> <p>A possible way would be to require that the originator and each organisational unit which reviews or approves the proposed change list the document in their areas or responsibility which will need to be changed and add this list to their “Review and Approval” document. After approval, each organisation unit is then responsible for carrying out the change to the documents and reporting the successful completion. For changes that require customer and/or regulatory approval a proper control strategy should be in place. Batch disposition should be pre-defined in the change control approval.</p>

13.15	<p>The intention of this Sub-section is that there should be a review of the effect of the introduced change upon the products effected:</p> <ul style="list-style-type: none"> a) be it by a process change, b) be it by a change in the testing procedure, c) be it due to changes in other factors which may affect the quality of the products. <p>As this is an activity, it should be recorded that such a review has taken place, and the conclusions drawn should also be recorded. (See also the Key Words in § 13.16 and §13.17).</p>
13.16	<p>In the ICH Expert Working Group it was accepted that there would be a large number of compounds, in particular inorganics which would still exhibit the same stability profile, even if the process had been considerable changes. Thus, there is no need <u>always</u> to add samples from the modified process to the stability monitoring programme.</p> <p>This paragraph not only applies when there are "process" changes, but other changes too, (such as the improvement to an analytical method resulting in the detection of a previously unknown breakdown product) could also affect the retest or expiry date and thus this paragraph was widened to include all critical changes, and this needs to be considered.</p> <p>This paragraph is only applicable when there are critical changes (and as "critical" has now been clearly defined, (See the Glossary in the ICH Q7 document GMP for APIs). Thus, not every change which will be reviewed under the CCS will fall into this category. Being in mind the definition of "critical" it is essential to remember that if the predetermined limits are not held, particularly if they are revised, and this results in the API not meeting its specification then these limits are critical. Under these circumstances the potential effect upon the stability should be very carefully evaluated. It is expected that the "evaluation" should be recorded, as should the conclusions as to whether additional stability testing is necessary. This record should obviously contain some scientific justification for the decision taken,</p> <p>This may take the form of a short statement, (e.g. "the original compound is stable for over 4 weeks at 80°C and thus the increase in the drying temperature to 65°C is unlikely to cause additional product breakdown, and no increase in the known or unknown impurities was detected") for it is not expected, nor should it be required that such scientific justification will require a full written discussion of what might possibly occur.</p> <p>Documentation for the potential impact to stability is stated on the change control evaluation form. The type of stability support (accelerated, extra yearly monitoring stability sample, no stability, ...) should be justified and documented.</p>
13.17	<p>It is not necessary to inform every dosage form manufacturer who has ever bought the product about the change. If there has been no supply of the product to a dosage form manufacturer over a longer period of time, the exchange of information should be re-evaluated (unless such information flow was part of the original agreement with such users).</p> <p>Informing dosage form manufacturers or any customer according to the Quality Agreement in place.</p> <p>Emphasis is placed on "procedures" (as it is assumed that if specification limits were changed the authorities would need to approve this, but may not even need to be informed about changes to "procedures"). The selection criteria is that the change can</p>

impact upon the quality of the API. Under such circumstances current users should be informed.

The words "impact the quality" should not be confused with "meeting the specification". Only too frequently in the past have dosage form manufacturers discovered that although the purchased API met the pharmacopoeia or other agreed specification, nevertheless its behaviour during subsequent processing to a dosage form was quite different. This is because there are still too many physical characteristics of an API which cannot easily be routinely measured. Under these circumstances, if the change is in the final step of the API manufacture and involves a change of equipment, solvent, isolation or purification conditions, it is advisable to contact key customers before introducing the change and provide demonstration ("Trial") material for experimental use. In this way, the API manufacturer not only avoids the potential loss of a customer, but also the need to reverse an already approved change.

Chapter 14 Rejection and Re-use of Materials

14.1 Rejection

This chapter is introduced because the concepts explained therein were necessary to avoid having auditors or government inspectors treating the reworking (or reprocessing) of APIs in the same way as the reworking (or reprocessing) of medicinal products were being treated.

There is an essential difference between the reworking (or reprocessing) of a chemical such as an intermediate or an API and the reworking (or reprocessing) of a physical mixture such as a medicinal (or drug) product. In the case of chemicals, the techniques of reprocessing or reworking have been used for centuries now to purify substances and remove impurities, whilst the reprocessing (or reworking) of a medicinal (drug) product rarely results in a purer product and may even result in a product with a shorter shelf life or lower bio-availability.

14.10 The intention of the wording is that this section applies only when there is an "established specification" for an intermediate, i.e. the section should not be applied when the intermediate is "monitored" to ensure that the use criteria for the next step (e.g. less than 0.5% free ketone) are met, (because in such cases the process step may be continued for a length of time till the use criteria are met). Similarly, the paragraph can only be applied to intermediates which are sufficiently long-lived that they can be held until the tests have been completed, even if such intermediates have not been isolated.

When material has actually been found not to meet specification simply retaining this material in quarantine is insufficient (except for material being under OOS investigation), but it specifically needs to be identified (i.e. physical or in the computer stock lists) as "DOES NOT MEET SPECIFICATION". Some companies actually place a red "Rejected" label on the containers waiting for a final disposition decision (reprocess, rework, destroy for API's and intermediates or further processing for intermediates only), but in such cases, there should be an SOP which indicates that a "Rejected" label does not automatically mean that the material has to be "Destroyed".

The material can be given a special status in the Material Management computer system to indicate that it is not in Quarantine awaiting test, but has already been tested and found deficient. Where such a computer system is not available, then management tools, such as stock cards, and even the containers themselves, need to be marked so

that it is seen that the material is "On Hold" and some companies use this term to denote such a quarantine status).

The statement "can be reworked or reprocessed" replaced the requirement that such material should be "rejected". In the cases of intermediates, further processing is one option of treating materials not meeting specification. One possibility which was not specifically mentioned, is that of actually using the batch of rejected material in the process without reworking or reprocessing it. ICHQ7 might be so interpreted to mean that intermediates which do not meet specification can still be released under quarantine for use in the next process step, and the "completion of the evaluation" including regulatory impact, can be carried out at the end of the process, i.e. a check is made whether the detected deviation from specification has no effect upon the final product quality. If such a procedure is permitted by the company's SOPs then there should be the requirement that such a step be classified as a "Concurrent Validation" step, because it will rarely have been covered by the normal prospective validation activities.

As there is no clear -instruction of "Rejected" in the Guide it is left to each company to define its' own policy on this topic in writing. The policy should state that if materials are truly "rejected" i.e. cannot be treated in any other way, apart from permanent disposal, then a record should be maintained of when and how this disposal was carried out.

14.2 Reprocessing

14.20 The very essence of this section is found in the words "repeating a step or steps that are part of the established manufacturing process is generally considered acceptable". This positive statement thus indicates to auditors and even governmental inspectors that (possibly in contrast to medicinal products) repeating one or more steps from the already established process is not objectionable.

The essential element of REPROCESSING is that it is not a deviation from an existing-described process.

§ 14.10 covers the situation where material does not conform to established specifications whilst in this paragraph the concept is widened to also permit reprocessing of material even if it originally met the established specifications. This later situation could arise when remainders of a batch (often called "tailings") are mixed with other tails and reintroduced to the process, (for example being re-dissolved and re-crystallised out) without being part of the validated process. This reprocess is permitted. The current industry practice is to validate such reprocessing unless justified by a risk assessment and documented.

APIC advice is to consider the need for reprocessed batches to be put on stability. For example, the reason for reprocessing, comparison of the impurity / degradant profile to the parent batch. The need not to add to a stability programme should form part of the change control for the reprocessing activity.

The examples given are only examples of typical reprocessing steps and reprocessing is NOT limited solely to these examples.

It is important to remember that regular reprocessing of materials is often an indication of a process not running "under control". Certainly, when the majority of the batches produced within a specific time frame need to be reprocessed, this is a clear indication of the inadequacy of the original process or failures in the quality management system. Consideration should be given to making reprocessing part of the normal

	<p>manufacturing process depending on the frequency of occurrence due to the same root cause.</p> <p>Initial reprocessed batches should be included in the stability program (usually one batch per type of/or reason for the reprocessing). Further reprocessed batches may be included in stability testing based on a risk assessment.</p> <p>Companies are moving away from reprocessing of batches in compliance with the specifications that reaches its retest period. If companies decide to continue this practice on a risk assessment based approach this should be supported with sufficient stability data and consider regulatory impact. There should be a procedure in place to support and document this practice.</p>
14.21	–
14.22	

14.3 Reworking

14.30	<p>Reworking involves another process which is not be covered by the original process description. Rework batches cannot be released until respective board of health approval has been obtained for the reworked process. ". The only exception to this rule would be if "alternative processes" had been approved and it is clear that material originally made by the one process could be "reworked" using the alternative and approved process.</p>
14.31 and 14.32	<p>The detail given in these two sections again indicates that if material is "reworked" a much deeper assessment should be made of the resulting product and the advice that Concurrent validation is a suitable means of dealing with "reworking" only underlines the fact that it would be insufficient solely to check the reworked material against the original specification, due to the possibility of that reworked material may contain new impurities or may have different physical properties such as crystal structure. This is very rarely the case with reprocessed material and thus this § 14.31 gives advice which is specifically appropriate for reworked material.</p>

14.4 Recovery of Materials and Solvents

14.40	<p>The quality of the recovered materials should not negatively impact the final quality attributes of the API (e.g. introduction of nitrosamines impurities or their precursors should be evaluated)</p> <p>Recovered materials DO NOT have to meet the same specification as the original materials, and although in most case the specifications will be broader than for original product. This may not always be "appropriate", and a tighter specification may be necessary to prevent difficult to remove impurities being enriched through the process and/or to avoid new impurities be introduced in the manufacturing process.</p> <p>Although the examples of "recovery" only include process steps which arise from the original process, nevertheless it is acceptable to recover APIs themselves, irrespective of their physical form, e.g. recovery from a medicinal product itself.</p>
14.41	<p>Specific approval is also given for recovering solvents, which not only makes economic sense, but is environmentally friendlier. There is NO REQUIREMENT that recovered solvents need to meet the same specification as the original materials, and although in most case the specifications will be broader than for original product, this may not always be "appropriate", and a tighter specification may be necessary to</p>

	prevent difficult to remove impurities being enriched through the process and/or to avoid new impurities be introduced in the manufacturing process.
14.42	<p>The important words in this paragraph are "adequate testing". How adequate the testing needs to be will depend on the projected use of the recovered material and the type of impurities the recovered process may originate (e.g. nitrosamines). Recovered solvents only being reused in the same process, i.e. being recycled, may need less testing than those being recovered and used in totally different processes. In the former case it might be adequate to solely check ID (e.g. refractive indices or specific gravities) and maintain these within an accepted range whilst in the latter case it may even be necessary to quarantine the recovered solvent until a whole batch of chromatographic or other tests have been completed. There is however no specific requirement that ALL recovered solvents need to be quarantined before reuse.</p> <p>The test regime should be justified. The criteria of "suitability" does not necessarily mean meeting the original specification, (as is discussed in § 14.41 above).</p>
14.43	<p>The documentation required should be GMP compliant. (e.g., batch production record, ERP, logbooks, inventory control ,.... See chapter 6). In cases when solvents are continuously recovered in a campaign or in continuous production it may only be possible to record how much new solvent is being added in what period of time (for continuous processing) or the number of batches (for batch production) to make up for losses caused by the process.</p> <p>The number of times solvent recovery can be performed before using again fresh solvent should be scientifically justified.</p> <p>. Traceability of recovered materials must be in place.</p> <p>If recovery of materials is outsourced it should be part of supplier qualification.</p>

14.5 Returns

<p>It is important to realise that this Section (14.5) equally applies to Agents, Brokers, Traders, Repackers and Relabelers, as stated in § 17.80.</p> <p>If outsourced companies are used who physically treat APIs, e.g. micronizers, or granulators This section applies to such companies also.</p>	
14.50	<p>When material has been returned, only transferring this material in quarantine is insufficient, but it specifically needs to be labelled (i.e. physical or in the computer stock lists) as "RETURNED". Some companies actually place a prominent "RETURN" label on the containers but care needs to be taken which would later be replaced with the label indicating the decision taken, e.g. "RELEASED for REPROCESSING" or "RETURN to ORIGINAL MANUFACTURER".</p> <p>The second precaution is to quarantine the materials physically separated from other material.</p> <p>In addition to the physical segregation, the material can be given a special status in the Material Management computer system to indicate that it is not in Quarantine awaiting test, but returned material. Where such a computer system is not available, then management tools, such as stock cards, and even the containers themselves, need to be marked so that it is seen that the material is "Returned Material"</p>
14.51	<p>The storage and shipping conditions the returned material must be taken in consideration for the disposition. Although in some cases, where the material is known to be very stable, (e.g. stable after 6 months under continuous storage at 40°C) there</p>

	<p>may be little doubt as to the quality. If this risk is identified such material SHOULD NOT be returned to the market.</p> <p>The process for the disposition decision should be defined in a procedure and product integrity needs to be ensured by considering topics like: the presence of the original seal, damage of primary packaging, labels, data loggers, storage conditions at the client, need for supplementary testing ...</p> <p>In the return is due to a commercial quality related complaint the potential impact to remaining or distributed material of the same batch should be part of the assessment.</p> <p>As this Section also applies to Agents, Brokers, Traders, Repackers and Relabelers who very rarely will be in the position to reprocess or rework material they will need to return it to the original manufacturer for such steps to be carried out. It is thus ESSENTIAL that Agents, Brokers, Traders, Repackers and Relabelers have a good traceability system, (as required by § 17.20) that they can determine who was the original manufacturer of the returned material.</p>
14.52	<p>The disposition decision (use or disposal) of the returned material can be reprocess, rework (or even "recovered"), released or rejected and destroyed</p> <p>Documented traceability is needed off all activities performed from receiving to disposition decision.</p>

Chapter 15 Complaints and Recalls

15.10	<p>The complaint investigation has to include the impact assessment of other batches potentially involved from the same product or different product(s) (multipurpose facilities).</p> <p>A period to close complaint investigations should be defined. If not possible to close the investigation timely an interim report should be prepared.</p>
15.11	-
15.12	Complaint records trend may be performed at least in the Product Quality Review or Quality System periodic review.
15.13 – 15.15	<p>In the scope of ICH Q7 (see ICH Q7 Q&A document) a recall can be defined if an API/Intermediate batch is already shipped outside the manufacturer's control and has to be called back from one or more customer due to an identified quality defect which makes the API/Intermediate or resulting finished dosage form unsuitable for further use/processing).</p> <p>In the event that the release status of a distributed API can be questioned the API manufacturer should be able to trace all parts of the batch in question which may have been distributed. or is still stored on site.</p> <p>The API manufacturer should have a procedure describing the process and responsibilities related to recalls/product (API) traceability, and should be able to document that batches can be traced and reconciled. Key personnel involved should be identified. Likewise, the responsibility for notifying customers and local authorities, if applicable, should be addressed.</p>

The recall process should be assessed for its robustness on a periodical basis. It is an option to include a Mock recall exercise in the site internal audit programme.

The concept of recall in its **original** meaning does not really apply to API manufacturers as they are never able to recall the finished dosage form from pharmacies, hospitals, distributors etc. This is the task of the Marketing Authorization Holder (MAH). Even notifying local and national health Authorities in case of life threatening situations can only be made in tight cooperation with the MAH, as they are the ones who distribute the finished dosage form to the market.

Chapter 16 Contract Manufacturers, including laboratories

Although the word "manufacture" was defined in the ICH Q7 GMP Guide to mean "all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and **related controls**", nevertheless the words "and laboratories" were added to the title of this chapter to make it perfectly clear that this chapter also applies to any laboratory which might carry out any analysis for the API manufacturer according to a specific request or agreement.

Related controls include any activities or services necessary to support production (e.g., maintenance, calibration, etc.). 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.

If a contract lab is used for products supplied to the US, FDA is requesting the registration number of the contract lab.

16.10 The contractor should take specific measures to prevent cross contamination, such as validating the cleaning procedures, using dedicated facilities where necessary, etc. Maintaining traceability should include knowing what materials were received, released and when, how and where were they processed, and when were they packed, labelled and stored. In order to assure maintaining traceability this requirement could be specified and agreed in a formal quality agreement.

16.11 Contract manufacturers evaluation should follow the supplier's qualification procedure to assure that contractor meets the GMP requirements for the contracted activities.

The contractor evaluation should include but not limited to the assessment on the adequacy of process equipment including laboratory equipment and facilities and quality system in place, type of certifications available.

A risk based approach should be taken to determine the type of audit (paper based if enough information and knowledge on the contractor is available or an on-site audit).

16.12 The supplier contract should clearly define the need for technology transfer (if applicable) and the responsibilities of each party.

A quality agreement should be in place to define the GMP activities and responsibilities as defined in the APIC guideline on Quality Agreements.
http://apic.cefic.org/pub/APIICQAGuidelinecomplete_new_final2.0_20171102_cleane

	d.pdf
16.13	As was pointed out in § 16.11 the type of audit can be a paper audit or on-site audit based on the risk of the activities contracted. The quality agreement should clearly define the frequency of the audits under the scope of the continuous evaluation of the contractor.
16.14	Chapter 16.14 is self-explained
16.15	<p>The intention of this paragraph is to ensure that the ORIGINAL records of any manufacturing activity (including laboratory testing) should be retained by the contract acceptor. If the contract giver wishes to have records of activities carried out, COPIES of the original records should be supplied. Such copies are often specifically marked by the contract acceptor to indicate that these are copies.</p> <p>Such records should be stored at the contract acceptor at a minimum according to the guidance given in Q7, § 6.13. (in accordance with the agreed document retention schedule).</p> <p>All Data Integrity requirements must be implemented including archiving, retrieval, periodical review and disposition of all data over the life cycle of the product.</p>
16.16	<p>This statement is essentially already covered by the requirements of § 16.10, - complying with GMP - because this also means that the contract acceptor has to comply with Chapter 13 Change Control.</p> <p>Contract manufacturer should not make changes to manufacturing process with impact on product quality and/or regulatory impact without approval of the contract giver, including the use of a different site under the responsibility of the same contract manufacturer. This should be clearly described in the quality agreement.</p>

Chapter 17: Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

17.1 Applicability

17.10: "Possession" means legal ownership, this section does not apply to transport companies who simply move the API or intermediate"

Procedures and controls for GDP at transport companies should be in place see:

APIC Statement on GDP:

<https://apic.cefic.org/pub/APIC-StatementGDP-201710.pdf>

Eudralex document GDP for API's:

[https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321\(01\)&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321(01)&from=EN)

See also: ICHQ7 Q&A chapter 17 question 1

17.11: Current expectation are that if the API or intermediate is re-packed or re-labelled the trader etc. should perform a documented risk assessment and determine which sections of Q7 are applicable to their activities. Section 13, Change Control and an appropriate Quality system are always applicable to all operators and their operations.

Extract from: EUDRA GMDP: <http://eudraqmdp.ema.europa.eu/inspections/loqonGeneralPublic.do>

In the EU, manufacturers, importers and distributors of active substances are required to register their activities with the National Competent Authority of the Member State in which they operate.

In the EU, a certificate of Good Distribution Practice (GDP) is issued to a wholesale distributor by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the wholesale distributor complies with Good Distribution Practice, as provided by European Union legislation. If the outcome of the inspection is that the wholesale Distributor does not comply a statement of non-compliance may be entered into EudraGMDP. GDP certificates and statements of non-compliance may be issued to wholesale distributors of medicinal products and distributors of active substances.

Link to verify if a company is registered in the US FDA database :

<https://www.accessdata.fda.gov/scripts/cder/drfs/default.cfm>

FDA guidance on how to register:

**INSTRUCTIONS FOR FILLING OUT FORM FDA 356h – APPLICATION TO MARKET A
NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE**

In case of non-compliance a risk assessment by the distributor contractor is needed to support ongoing use of the distributor (in any case the QP of the Manufacturing Authorisation Holder (MAH) has final responsibility)

17.2 Traceability of Distributed APIs and Intermediates

17.20	<p>This Section needs very little interpretation. The EWG of ICH Q 7 gave a very detailed listing of the documents which need to be retained in order to assure the traceability of any material passing through the hands of an Agent, Broker, Trader, Repacker, etc.</p> <p>Although the word "should" has been used in this section, it should be understood as "must" and they need to fulfil the ICHQ7 requirements.</p> <p>It should be noted that the wording "retained and available" means not only retained and made available to the authorities but also to the customer of the Agent, Broker, Trader, Re-packer, etc., on request.</p> <p>It is essential that the identity (i.e. name) and the address of the <u>original manufacturer</u> be given to the customer (see also § 17.61. If traceability is not fully understood and available, the product should not be accepted until the investigation assures traceability is fully understood and the original manufacturer is part of the qualified supplier list.</p> <p>It is already known by many Brokers, Traders, Re-packers, etc. that one should not accept at face value certain names and addresses of companies provided by state controlled export agencies, as their practice of changing the source of the API depending on which state company has stocks available are well known.</p> <p>The QP responsibilities in EU as described in Annex 16 of the Eudralex Vol. 4 are also applicable on traders, brokers, distributors, Re-packers etc. The inclusion of the wording "authentic" Certificates of Analysis is to indicate that it is <u>not acceptable</u> to copy the Certificate of Analysis of the original manufacturer onto the letter heading of the Agent, Broker, Trader, etc.</p> <p>It is a current expectation that besides the documents listed in the ICHQ7 there should be a written statement on regulatory and quality requirements such as: TSE/BSE – heavy metals/catalysts – residual solvent ... from the manufacturer if applicable</p> <p>In general, the customer should receive all necessary information to fulfill his Regulatory and Legal obligations.</p>
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17.3 Quality Management

17.30	<p>It is a current expectation that the Quality Management System implemented should fulfill all requirements as defined in ICH Q7 chapter 2 to assure that a system is in place to control all GMP activities and GDP guidelines like: Eudralex document GDP for API's:</p> <p>https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321(01)&from=EN</p>
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17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.40	<p>See 17.11 If the API or intermediate is re-packed or relabelled the trader etc. should perform a documented risk assessment and determine which sections of Q7 are applicable to their activities. Section 13, Change Control and an appropriate Quality system is always applicable to all operators and their operations</p>
17.41	-

17.5 Stability

Requirements as stated in section 11.5 of the ICHQ7 are applicable and should be applied.

17.6 Transfer of Information

17.60	<p>This section is included to ensure that information which would normally be transferred by the API manufacturer to the dosage form manufacturer (In General the customer should receive all necessary information to fulfill his Regulatory and Legal obligations) as required under § 13.17 is transferred instead to the Agent, Broker, Trader, Re-packer, etc. if applicable.</p> <p>The meaning of "all quality and regulatory information received from the API manufacturer" means much more than the information listed in § 17.20 and would cover any changes made by the manufacturer to the process, the specifications (specifically the deletion of a test parameter) the test methods, the retest date, storage conditions etc.</p>
17.61	<p>This is an unequivocal statement, specifically inserted in the ICH Q7 guide at the request of the dosage form manufacturers and supported by the authorities. It makes it clear that the process of covering up the source of APIs, ("neutralising"), is no longer acceptable. It is an expectation that traceability must be assured over the full supply chain and a system should be in place to control supply chain integrity.</p>
17.62	<p>The authorities expect that Agents, Brokers, Traders, Re-packers, etc. will not only comply with this guide but also actively cooperate with the authorities to clarify matters which only the Agents, Brokers, Traders, Re-packers, etc. may be aware of. Thus, when the authorities have reasons to involve Agents, Brokers, Traders, Re-packers, etc. in their investigations, the latter are obliged to respond to "a request" in a timely manner. Agents, Brokers, Traders, Re-packers, etc. should therefore, in order to minimise any risks to patients, reply promptly and fully to such requests for information from the authorities.</p>
17.63	<p>If a request is made to an Agent, Broker, Trader, Re-packer, etc. for a Certificate of Analysis <u>all the requirements</u> listed in § 11.4 (Certificates of Analysis) <u>must be met</u>.</p> <p>In particular, the requirement that if NEW analyses have been carried out, (not only by a Re-packers or Re-labeller but also by a broker or agent as well), these should be given</p>

	<p>in a NEW Certificate of Analysis showing the name and address of the laboratory that carried out the NEW tests. It would <u>not</u> be acceptable to replace the original values certified by the original manufacturer by the new values from the re-testing laboratory but rather TWO separate Certificates of Analysis should be provided to the customers, the Certificate from the original manufacturer (with a translation when appropriate) and the second Certificate from the re-testing laboratory.</p> <p>If the re-testing laboratory takes over ANY TEST RESULTS from the original manufacturer into the NEW certificate, this should be clearly indicated for each test result taken over. (This is necessary to check, when necessary, where the raw data may be located - and thus audited - in order to confirm the authenticity of the certified results).</p> <p>It should be pointed out that if an Agent, Broker, Trader, Re-packer, etc. involves a contract laboratory in any testing of any materials handled by them, the requirements of Chapter 16 (Contract Manufacturers including Laboratories) are to be followed.</p>
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17.7 Handling of complaints and recalls

17.70	It is an expectation that critical complaints and other complaints as agreed in the Quality Agreement and requests for recall should immediately be informed to the related customers and suppliers. This should be part of the <u>Quality Agreement</u> .
17.71	<p>It is an expectation that the investigation outcome and corrective/preventive actions defined for complaints as described in 17.70 should be informed promptly to the customer(s).</p> <p>And it is also an expectation that a system should be in place to assure a recall of all products involved can be accomplished in a timely manner.</p> <p>A regular Mock recall audit/exercise, on the most complex distribution system, is advised to be performed and documented.</p> <p>Legal time frames for reporting potential recalls to Health Authorities and customers should be followed. See chapter 15.</p>
17.72	Records of complaints should be maintained (according to document retention requirements as specified in section 6.12) at location and should become part of the quality management review (ICH Q10, EU part III) in order to evaluate trends or product related issues so that decisions can be made on appropriate preventive actions if required.

17.8 Handling of returns

17.80	It is an expectation that system should be in place to evaluate the disposition decision of returned materials. Control of the presence of the proper unique sealing for container integrity and information about storage conditions outside control of the agents, broker... should be available for the decision-making process. If the proper unique seal and storage conditions are not available or known the disposition decision should consider rejecting and destroying the product.
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Chapter 18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

18.1 General

The explanations to clarify the “how to do” of this chapter is given from the perspective of “classical fermentations”	
18.10	No further explanation needed; note that “In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.”
18.11, 18.12	Definitions for “biotechnological processes” and “classical fermentation” are given, that cover differences between these two types of fermentation processes, e.g. regarding type of organisms used and products obtained.
18.13	This subchapter refers to the need to control bioburden, viral contamination and/or endotoxins during the fermentation and recovery steps. This need is more outspoken for products from biotechnical processes than for those from classical fermentations, unless the API produced will be processed further to a sterile drug product. Additional guidance is given in later subchapters.
18.14	In some classical fermentation, the start of a fermentation is not always by making use of a vial of the cell bank, but by using it for the inoculation as part of a previous, successful fermentation
18.15	Fermentators need not always be placed in areas that are supplied with air of a controlled quality (Grade C, as defined in “The rules governing medicinal products in the European Community”). Areas of level I as defined in ISPE-guide Bulk Pharmaceutical Chemicals could be appropriate.
18.16	Parameters for controlling critical operating parameters during fermentation could be the following, but are not limited: temperature, oxygen concentration, pH, agitation rate, concentration of critical starting materials or Excipients etc. The level of protection of the intermediate or API is dependent on the nature or future use of the intermediate or API and could be seen in relation to the way the downstream processing is performed. Some APIs have an inherent potential as antibacterial or preservatives. For classical fermentations, normal hygienic conditions should be in place, in that case there is no need to monitor bioburden and endotoxin levels.
18.17	–

18.2 Cell Bank Maintenance and Record Keeping

General remark: It is usual to maintain a Master Cell Bank (MCB) and a Working Cell Bank. By maintaining a MCB many production runs can be done with the same organism	
18.20	No further explanation needed, but as stated in 18.14, the use of a cell bank for a next fermentation is not always necessary.
18.21	–
18.22	–

18.23	For classical fermentation's it will often be difficult to establish the usage period of a cell strain before it is used, however cell banks can be monitored to determine suitability for use by recording the productivity (in a quantitative and qualitative way) of the organism.
18.24	–

18.3 Cell Culture/Fermentation

18.30	–
18.31	–
18.32	In case a company performs more than one fermentation process, precautions should be taken during handling of cell cultures that prevent contamination. Examples could be: dedicated inoculation areas, dedicated personnel or gowning and appropriate cleaning procedures for utensils.
18.33	–
18.34	No further explanation needed; see 18.42.
18.35	An additional reason for sterilising culture media could be the quantitative aspect of the fermentation.
18.36	Procedures that determine the impact of the foreign growth on the product quality can take into consideration the established experience a company may have with fermentations that have shown foreign growth before. General experience from companies engaged in classical fermentations learns that foreign growth does not necessarily have a negative impact on product quality.
18.37	–
18.38	–

18.4 Harvesting, Isolation and Purification

18.40	With reference to the remark in 18.15 the environment in which the downstream processing takes place need not always be supplied with a controlled quality of air. Also in this case normal hygienic conditions should be in place.
18.41	–
18.42	–
18.43	See 18.40 for products of classical fermentation.
18.44	–

18.5 Viral Removal/Inactivation steps

This subchapter is applicable to “biotechnological processes” only.	
18.50	–
18.51	–
18.52	–

18.53	–
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Chapter 19 APIs for Use in Clinical Trials

19.1 General

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19.10	All previous chapters not referred in this section are considered applicable for APIs for use in clinical trials.
19.11	<p>The quality system in place in development phase should be appropriate and proportionate to each stage of the Product lifecycle, recognizing the differences among, and the different goals of each clinical stage.</p> <p>To achieve this goal manufacturing activities should be carried out under an increasing set of GMP controls as process performance qualification (PPQ) phase is approached. The resulting accumulated knowledge during the development phase will be the basis for the determination of proven quantitative parameters, which will guarantee safety and reliability of the process, allowing transfer from a Research and Development (R&D) environment to a routine manufacturing environment.</p> <p>Appropriate GMP system should be designed for development phases and risk management based on the following principles:</p> <ul style="list-style-type: none"> • Development should ensure that all products meet the pre-defined requirements for quality, purity and safety in each development phase; • During development phases all information /knowledge gain should be documented and retrievable; • The rationale for the controls being implemented or disregarded should be documented • All related quality activities should be defined and documented.

19.2 Quality

19.20	<p>The GMP requirements for development phase should be well-defined in written procedures or in a quality plan which should encompass all activities since raw material purchasing up to batch release, having in consideration the principles above. Organizational structure and resources should be included.</p> <p>It is expected that with the knowledge increasing the degree of controls and complexity be a crescendo from phase I up to phase III. In all stages Quality Unit should be involved.</p> <p>Personnel should have the education, experience and training adequate to perform their assigned function.</p>
19.21	Depending on the company organization, Quality Unit for Development can be independent from the Quality Unit for commercial products.
19.22	Analytical testing may be performed within other organizational units (e.g. manufacturing, R&D...) or by an outside contractor. In any case the area applicable

	<p>procedures should be followed. Personnel involved should be trained to mitigate cross-contamination that may negatively impact test results.</p> <p>All analytical results obtained should be recorded, checked and traceable (ALCOA principles are applied). To allow traceability, a defined batch identification system should be in place. This can be based on a product unique code and a correlative batch number. Traceability should be checked at appropriate intervals.</p>
19.23	<p>Raw materials, intermediates, packaging materials and APIs should be tested to confirm that they are suitable for the intended use. Specifications for all materials should be defined based on the level of process understanding, knowledge and risk management. It is expected that the specifications change from phase I to phase III. A procedure should be in place to document and justify specification changes (see 19.7).</p>
19.24	<p>Process and quality problems (e.g. deviation, OOS...) are expected to occur during development phases and should be considered as part of the process understanding. However, written procedures to handle quality problems should be available and followed as applicable, detailing how to address the issue depending on the concerned phase. The level of investigation should be commensurate with the stage of development, criticality (impact on product quality) and frequency of the occurrence.</p>
19.25	<p>A labelling system, in accordance with the identification system in place, should be applied to each substance/sample (see section 6.3).</p> <p>A master label should be prepared, approved and used. It should contain at least:</p> <ul style="list-style-type: none"> - The identification of the compound - Batch number - Storage conditions (see 19.82) - Retest date (see 19.82) - Safety information, as appropriate, for external transport - A note that the product is for investigational use or equivalent

19.3 Equipment and Facilities

19.30	<p>All equipment used in laboratory scale preparation should be appropriate to the intended use, in good working order, and clean.</p> <p>Qualification of lab and pilot scale equipment and utilities should be considered. At least IQ and OQ activities should be included in the qualification plan. Calibration against standards and maintenance (e.g. preventive, corrective, ...) should be performed at appropriate intervals and in accordance with approved procedures, to ensure reproducibility of the product preparation process.</p> <p>In multi-product facilities cleaning procedures and controls should be in place to ensure that no carry-over is observed higher than the admissible amount. Carry-over may be determined based on APIC guide on cleaning validation:</p> <p>http://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf.</p>
19.31	<p>See also Chapter 6.2. and 12.7.</p>

Cleaning procedures may be either specific or generic and should be developed as integral part of the manufacturing process to achieve an effective cleaning of the plant and equipment. When moving to the commercial manufacturing scale, the cleaning procedure may differ from the pilot scale due to business or environmental constraints.

Validation of cleaning procedures should be performed concurrently with the PPQ phase and can be completed during commercial manufacture.

19.4 Control of Raw Materials

19.40 A systematic approach for raw materials reception, testing and acceptance / release decision should be in place. Records should be kept allowing traceability of the materials used in manufacturing. Materials should be controlled (e.g. segregated) until be tested and release for manufacturing. They should be handled in way to prevent degradation or contamination.

19.41 Raw material specifications should evolve with the development of the process. It is acceptable that in earlier phases (e.g. Phase I) raw materials be accepted against certificate of analysis and/or use test at small scale. However, with the scientific knowledge and experience acquired during development phase specifications should change from supplier specification to be focused on relevant quality attributes and acceptance criteria to provide a better control of the material.

It is expected that suppliers are qualified at the time of moving to commercial scale

19.5 Production

19.50 Process documentation should contain references to raw materials, chemical reaction / isolation pathway, process equipment, process parameters, any unexpected occurrence or changes made during the course of the manufacturing, including the rationale for the changes. In-Process controls (IPC) are expected to be defined and even in higher number with the purpose to gain knowledge on the process and to determine the critical process parameters. It is admissible that with the experience and based on scientifically sound justification the number of IPCs be reduced up to Phase III, where the synthesis route should be fixed.

19.51 Expected yields should be defined based on the knowledge and experience and updated across the development phases. Excursions to the yields should be recorded in the batch production record. No formal deviation and investigation is expected to be issued.

19.6 Validation

19.60 No PPQ is required during development phase as the manufacturing process is not fixed. However, a PPQ strategy should be defined at the end of Phase III.

19.61 The information gathered during the development phase will become the foundation for the validation of the commercial process, including cleaning process validation.

19.7 Changes

19.70	Changes are part, as described above, of the development phase. Changes and its rationale should be recorded and traceable for late information but may not be subjected to a formal change control system. A process should be in place to communicate changes to Customer, when applicable.
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19.8 Laboratory Controls

19.80	<p>At early stages, product characteristics are often unknown. Analytical methods should be developed in parallel with the manufacturing process to gather increasing knowledge of the product quality profile.</p> <p>Testing methods should be scientifically sound (e.g. specific, sensitive and accurate). Analytical evidence should be established and documented to support the suitability and reliability of the method. All performed changes should be documented with the justification and rationale.</p> <p>Analytical methods should be fully validated latest at the time of PPQ batches. The resulting analytical data will become the foundation for setting the raw materials, API starting materials, the intermediates and API specifications.</p>
19.81	Retain samples from each batch should be defined and followed according the procedure. It should consist of a representative sample in an adequate quantity to perform additional testing or investigation if required (e.g. twice the quantity necessary to perform the release testing, if possible). Retain samples of the API, should be stored at least two (2) years after release of the investigational medicinal product batch where the API was used (based on the EU No. 2017/1569 art 11).
19.82	Information gathered about stability of the product during research and early development phases should be used to define preliminary retest date and storage conditions,

19.9 Documentation

19.90	<p>Documentation generated during development phases should be retained in a GMP archive as commercial documentation.</p> <p>It is expected to document the information gained during process development (until Phase III) in a Process Development Summary Report or similar which should include trials and errors experiments and their related learnings. This document should be easily retrievable and be used as source of knowledge to support future process changes at commercial scale.</p>
19.91	It is expected to document the information gained during analytical development (until Phase III) in an Analytical Development Summary Report or similar which should include trials and errors experiments and their related learnings. This document should be easily retrievable and be used as source of knowledge to support future analytical changes during commercial production.
19.92	Records directly related to the manufacturing and the testing of the product should be retained for at least 2 years after the product approved or the clinical testing discontinued.

Chapter 20 Glossary

Please refer to the original ICH Q7 document for any definitions!

Chapter 21 ICH Q7 Q&A “how to do”

**INTERNATIONAL CONFERENCE ON
HARMONISATION OF TECHNICAL REQUIREMENTS
FOR REGISTRATION OF PHARMACEUTICALS FOR
HUMAN USE**

**Implementation Working Group (IWG)
on ICH Q7
Questions and Answers**

– for final agreement -

dated 14 April 2015

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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 GMPs at all stages of the 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 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), Quality Risk Management (ICH Q9), and Pharmaceutical Quality Systems (ICH Q10). GMP principles as described in ICH Q7 should be applied regardless 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 19) and for APIs manufactured by cell culture/fermentation (section 18).

Black is the ICH Q7 Q&A question

Light Black is the answer from the ICH Q7 Q&A working group

Blue is the APIC How to Do TF input on the ICH Q7 Q&A document

1 Introduction – Scope

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	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, 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, 5]; for master cell banks, see [ICH Q5B; ICH Q5D].
APIC	The evaluation if an appropriate level of GMP controls for the production of the API starting material is present should be based on the risk assessment and process knowledge of your process. Key topics to consider are: - The classification of the SM in your process (examples is it a Chemical, an Intermediate, a Penultimate, an API,...) to understand the depth of risk assessment to be applied - An appropriate robust quality oversight model (supplier qualification process)

	<p>is needed on the SM to ensure that the quality is understood, consistent and maintained. This will ensure any impact on the API quality is evaluated and if necessary appropriate control strategies implemented.</p> <p>- From APIC perspective it is recommended to have a quality agreement in place describing detailed roles and responsibilities between both parties.</p> <p>APIC Guide: http://apic.cefic.org/pub/QualityAgreementGuideline_final_200912_clean.pdf - Auditing/Inspections performance history</p>
2	Does ICH Q7 apply to manufacturing steps for the addition of substance(s) to an API (e.g., to stabilize the API)?
ICH	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 these mixtures [ICH Q7, 1.2, 20 – see Glossary for definition of ‘API’].
APIC	APIC’s position on API mixtures is described in: http://apic.cefic.org/pub/APIIC_API_definition_position_paper_final.pdf

2 Quality Management

1	What is meant by ‘quality unit(s) independent from production’?
ICH	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, 2.13].
APIC	Set up an independent reporting line from the Quality Unit to the company management. (Independent reporting line other than manufacturing departments/heads) The structure that gives the independent decision making should be proceduralised and described in personal Job Descriptions
2	Does ICH Q7 expect that the quality unit performs API release testing?
ICH	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. ‘Quality control’ in the ICH Q7 Glossary [ICH Q7, 20] refers to the activities, not the organisational structure. For examples of quality responsibility related to testing and release, refer to [ICH Q7, 2.13, 2.22, and 11.12]. Appropriate laboratory controls should be followed [ICH Q7, 11.10, 16.10] regardless of who performs the testing.
APIC	Typically API release testing is done in-house. However, in case the quality unit outsources release testing, i.e. a sister site or contract lab, the outsourcing QU needs to ensure and demonstrate an adequate oversight system is in place. The outsourcing QU has the final responsibility on the disposition decision. (ICH Q7 Chapter 16 should be applied) A quality agreement must be in place between both parties’ clearly defining roles & responsibilities.
3	Can other departments outside of the quality unit be held responsible for releasing raw materials and intermediates?
ICH	Yes. The quality unit is responsible for establishing a system to release or reject raw materials, intermediates, packaging, and labelling materials. This responsibility cannot be delegated [ICH Q7, 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,

	2.22(1)) as long as oversight and the overall responsibility of this system remains with the quality unit.
APIC	Delegated release responsibilities should be proceduralised and evaluated by the QU for example during an internal audit
4	<i>Does ICH Q7 expect that sampling be performed by the quality unit?</i>
ICH	No. ICH Q7 does not prescribe specifically who should perform the sampling [ICH Q7, 2.22]. However, the quality unit has responsibility for reviewing and approving sampling plans [ICH Q7, 11.12] and procedures. Sampling should be performed by adequately trained personnel [ICH Q7, 3.10] and be appropriately documented as per [ICH Q7, 6.52].
APIC	Delegated sampling responsibilities should be proceduralised and evaluated by the QU for example during an internal audit
5	<i>What should be the frequency of a product quality review?</i>
ICH	A product quality review is generally expected annually. Review timeframes 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 as per section [ICH Q7, 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, 2.50; ICH Q10, 2.6].
APIC	The frequency of a product quality review should be proceduralised and if not performed annually the rationale should be justified and approved by the QU
6	<i>Should the product quality review of results include trend analysis?</i>
ICH	Trend analysis is usually an important element in verifying the consistency of the process as part of the product quality review [ICH Q7, 2.50, 2.51]. Potential tools to use are described in [ICH Q9, Annex I.9].
APIC	Trend evaluation of quality reviews should be proceduralised. Trend evaluation in the annual product review should be mandatory for critical quality attributes and for critical process parameters as defined in the CPV (Continuous process verification) for: Final API's Critical intermediates Intermediates sold outside the control of the manufacturing company Contract manufactured Intermediates and API's require the contractor to generate the Product Quality review. The PQR needs to be provided to the contract giver in a defined time period as specified in the quality agreement The PQR of final API's should contain a statement on product stability. If there is a limited number of batches manufactured within the review period than historical can be used to aid the trending evaluation. In case there is no historical data available (example a new product introduction) an option is to plot the data versus the specification limits for the evaluation.

3 Personnel

1	<i>What is the intent of the statement in [ICH Q7, 3.12] ‘training should be periodically assessed’?</i>
ICH	In [ICH Q7, 3.12], the statement ‘ <i>training should be periodically assessed</i> ’ refers to a system to evaluate if personnel remain proficient and competent in their job tasks and responsibilities, and whether more frequent, additional, or new training is needed and recurring training is up to date.
APIC	<p>Effectiveness of training can be verified by a variety of means and should be embedded in your quality management system. (ICH Q10, 2.6) By direct (e.g. testing, questionnaire) and/or indirect means, e.g. individual observations, periodical assessment (usually annual) interview with supervisor, unconfirmed OOS, Internal Audits, deviations</p> <p>The need for GMP training should be periodically evaluated, conducted if needed and documented as part of the individual training programme of the employee. Each company should define the performance of each employee and his/her job based on their own training policy,</p> <p>Effectiveness of training is also applicable for contractors that perform GMP activities on side</p>
2	<i>Does ICH Q7 expect the use of a consultant and can a company delegate tasks and/or responsibility to a consultant?</i>
ICH	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 2.7, ICH Q7 2.2, 3.3].
APIC	<p>If consultancies are to be used they need to be evaluated, qualified and approved.</p> <p>The evaluation level should be risk based and related to the level of tasks to be performed. The review and approval of any GMP document should be under review of the Quality Unit.</p>

4. Buildings and Facilities – Containment

1	<i>When are dedicated production areas expected?</i>
ICH	<p>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, 4.40].</p> <p>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, 4.41].</p> <p>While ICH Q7 does not define high pharmacological activity or toxicity, these 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 S-guidelines, ICH E2E, 2.1.1], and the consequences of cross-contamination [ICH Q9, 4.3].</p>
APIC	<p><i>The supporting rationale to manufacture a product with high pharmacological activity or toxicity should be officially documented and approved.</i></p> <p><i>APIC advises to have a pre-meeting with your local HA to discuss and explain your risk assessment prior to introduce a product with high pharmacological activity or toxicity in a multipurpose facility.</i></p> <p>https://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf</p>
2	<i>To what extent can quality risk management be used in establishing appropriate containment measures to prevent cross-contamination?</i>
ICH	<p>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.</p> <p>Appropriate containment measures and controls [ICH Q7, 4.42] include but are not limited to the following:</p> <p>Technical controls (e.g., dedicated production areas, closed/dedicated HVAC system, closed manufacturing systems, use of disposable technologies, design of facility and equipment for containment and ease of cleaning)</p> <p>Procedural (organisational) controls (e.g., cleaning, personnel flow, environmental monitoring and training)</p> <p>Monitoring systems are important to check the effectiveness of the containment controls.</p>
APIC	<p><i>Besides cleaning, personnel flow, environmental monitoring and training also gowning, maintenance programs should be evaluated risk based</i></p> <p><i>Monitoring systems can be but not limited to:</i></p> <ul style="list-style-type: none"> - Alarms - airflow direction and pressure differential gauges - environmental testing program - trending contamination related deviations - temperature and humidity monitoring - periodically trend reports area performances

5 Process Equipment – Cleaning

1	<i>For dedicated equipment, is ‘visually clean’ acceptable for verification of cleaning effectiveness, (i.e., no expectation for specific analytical determination)?</i>
ICH	‘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, 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, 5.23, 12.7].
APIC	<p><i>“dedicated equipment” can be defined in various ways such as:</i></p> <ul style="list-style-type: none"> <i>- a reactor that is used solely for 1 API process</i> <i>- a reactor used for different intermediate steps of the same API.</i> <i>- a reactor used for different steps in the same intermediate or API</i> <i>- a reactor solely used for 1 stage in 1 process</i> <p><i>Whatever definition is used it should be documented and justified.</i></p> <p><i>https://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf</i></p> <p><i>For definition of dedicated facility see also ISPE base Guide: Active Pharmaceutical Ingredients second edition, June 2007</i></p> <p><i>When visual inspection is applied following points should be considered:</i></p> <ul style="list-style-type: none"> <i>- adequate lighting</i> <i>- fully dried</i> <i>- difficult to clean spots visually inspect able</i> <i>- use of cameras, endoscopy</i> <i>- limit of detection of visual cleanliness</i> <i>- dirty hold time / clean hold time</i> <i>- Campaign length</i>
2	<i>Should acceptance criteria for residues be defined for dedicated equipment?</i>
ICH	<p>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, 5.22, 5.23, 5.24, 5.25, 8.50].</p> <p>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, 5.21]. Where validation data has confirmed effective cleaning, cleaning procedures should be monitored at appropriate intervals [ICH Q7, 12.76].</p>
APIC	<p><i>Acceptance Criteria should be available for:</i></p> <ul style="list-style-type: none"> <i>- degradation products</i> <i>- detergents / cleaning aids</i> <i>- solvents</i> <i>- product</i> <p><i>Acceptance criteria should be based on:</i></p>

	<p><i>- acceptable level of carry over based on the process knowledge</i></p> <p><i>- suitable and validated analytical methods</i></p> <p><i>- Limit testing of Visual clean</i></p> <p><i>APIC cleaning guide: https://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf</i></p>
3	<i>Is it expected that equipment cleaning time limits be confirmed in cleaning validation?</i>
ICH	<p>Yes. Equipment cleaning is addressed in two sections in ICH Q7. While the cleaning validation [ICH Q7, 12.7] does not specifically address time limits for cleaning, [ICH Q7, 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.</p> <p>While ICH Q7 does not specify the need for time limits between equipment cleaning and use in the next process (clean hold time), [ICH Q7, 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.</p>
APIC	<i>Cleaning time limits should be documented and follow GMP requirements (deviations, changes, ...)</i>
4	<i>Is it expected that campaign manufacturing be addressed in cleaning validation?</i>
ICH	<p>Yes. The cleaning validation section [ICH Q7, 12.7] does not specifically address campaign manufacture. However, sections [ICH Q7, 5.23, 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.</p>
APIC	<i>Where significant carryover occurs between batches and particularly in the case of filter or dryer heels, it should be demonstrated that no unacceptable build-up of impurities or, where applicable, microbial contaminants is occurring (see 5.23 ICH Guide). This will also assist in determining the frequency of cleaning of equipment which is dedicated to the long term manufacture of one product</i>
5	<i>At product changeover, are both visual examination and analytical testing necessary to verify that equipment is clean?</i>
ICH	<p>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, 12.72-75]. Once the cleaning process is validated, routine monitoring of cleanliness of equipment at product changeover should include visual inspection [ICH Q7, 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.</p>
APIC	<i>The frequency of monitoring should be proceduralised based on the risk assessment</i>

6 Documentation and Records

1	<i>What is meant by ‘completely distributed’ in [ICH Q7, 6.13], which states that ‘records should be retained for at least 3 years after the batch is completely distributed’?</i>
ICH	<p>For APIs with a retest date, [ICH Q7, 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.</p> <p>In the case of APIs handled by agents, brokers, traders, distributors, repackers, and relabellers [ICH Q7, 17], ‘completely distributed’ refers to distribution of the received quantity of the batch of API.</p> <p>The intent of ICH Q7 is to retain records 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 three 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.</p> <p>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.</p>
APIC	Self explaining
2	<i>Does a batch numbering system need to be sequential?</i>
ICH	No, [ICH Q7, 6.51] says only that batch production records should have a unique batch or ID number.
APIC	The system to define unique batch or ID number should be proceduralised and understandable for the user
3	<i>Who is responsible for the issuance of batch production records?</i>
ICH	[ICH Q7, 2.3] does not specify who is responsible for the issuance of batch production records [ICH Q7, 6.5] as long as the issuance process is described in writing and approved by the quality unit [ICH Q7, 2.21].
APIC	A system should be in place that duplication is not possible without documentation of the rationale and QU oversight recreating documents must be <u>Justified</u> (original shown to be unfit for use) <u>Visible</u> (approved by the quality system example deviation and blanc document templates issued under control) <u>Verified</u> (true copy – current dating of copy) and <u>Retained</u> (original must be retained as evidence) The system should be proceduralised

7 Materials Management

1	<i>Does the phrase ‘grouping of containers’ have the same meaning in [ICH Q7, 7.20 and 7.24]?</i>
ICH	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, etc.) usually intended for ease of shipment and reconciliation. [ICH Q7 7.20] is referring to incoming visual examination of materials before acceptance into the facility under quarantine.

	The phrase in [ICH Q7, 7.24], 'grouping of containers (batches)' contains an additional word 'batches' because this section is addressing the need to establish batch traceability for the incoming material.
APIC	self explaining
2	<i>What is expected in terms of evaluation of suppliers of materials?</i>
ICH	Different phrases are used to describe the expectation for evaluation of suppliers of materials [ICH Q7, 7.11, 7.12, 7.31], including traders, if any. [ICH Q7, 7.12] states that all materials are purchased against a specification and from suppliers approved by the quality unit [ICH Q7, 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, 7.31]. More extensive evaluation is needed for suppliers of those materials classified as 'critical' [ICH Q7, 7.11].
APIC	Perform Risk assessment based on the intended use, criticality and knowledge of the supplier to define the evaluation strategy The supplier selection, evaluation, qualification and monitoring process should be proceduralised – if all evaluation requirements that are required according to your own procedure are not met, than the continued use of the product should be risk assessed and the final decision documented. APIC guide on supplier qualification: http://apic.cefic.org/pub/GuidelineSupplierQualification_200912_final.pdf Examples of materials in scope are: - Product contact materials (filters, centrifuge bags, equipment and piping,...) - Gasses (Nitrogen, compressed air, hydrogen, ...) - Primary packaging components - Raw materials (Solvents, reagents,...) - Starting Materials
3	<i>What is meant by 'full analysis' [ICH Q7, 7.31] on batches of raw materials to qualify a supplier?</i>
ICH	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, 7.31]. A raw material supplier's Certificate of Analysis (CoA) may not necessarily align with the user's specifications.
APIC	Only after a thorough evaluation during the risk assessment process, should reduced sampling and testing be considered.
4	<i>Are on-site audits required in the evaluation of suppliers?</i>
ICH	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, 7.11, 7.31].
APIC	APIC guide on supplier qualification: http://apic.cefic.org/pub/GuidelineSupplierQualification_200912_final.pdf A documented risk assessment is needed to determine the necessity to perform an on site audit as part of the supplier evaluation/qualification - Audits are a useful tool /part to understand the quality culture implemented at the supplier and to support the control strategy of the purchased material. If audits are used auditors should be trained in auditing techniques and have knowledge of the quality standards/expectations of the materials being evaluated. A system must be in place to qualify auditors

	<p>APIC 3rd party audit certification: http://apic.cefic.org/publications/TheAPICAuditProgrammeV3_update201207.pdf</p> <p>The frequency of re-auditing suppliers is based on the supplier performance and criticality. (including contract lab qualification)</p> <p>In case your risk assessment requires an audit but the supplier refuses the qualification of a new supplier should be evaluated. If the original supplier is still used to avoid drug shortages during this qualification process a justified documented rationale supporting the ongoing use must be available (based on vendor questionnaire, full supply chain traceability, extended testing if needed, inspection/audit history, historical performance and quality,.....)</p>
5	<i>Which tests are considered to be identity tests?</i>
ICH	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, 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, 7.32].
APIC	Self explaining
6	<i>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?</i>
ICH	<p>Manufacturing and labelling of raw materials for use by API manufacturers is outside the scope of ICH Q7. As such, 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 of [ICH Q7, 20], applies specifically to the API.</p> <p>API manufacturers may re-evaluate [ICH Q7, 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.</p>
APIC	<p>The process for extending the expiry or retest date of a raw material should be proceduralised and risk based considering (but not limited) the following:</p> <ul style="list-style-type: none"> - nature of the raw material (ionic salt versus complex organic molecule) - analytical method valid for intended use (capability and need to detect degradants) - available scientific literature - Supplier information - analytical data and original retest period <p>The frequency and time period of potential extensions should be specified in a procedure</p> <p>For highly toxic/hazardous materials that are not initially tested can be extended based on supplier information and use test results.</p>

8. Production and In-Process controls

1	<i>Can yield ranges defined for the first batch differ from latter batches within a campaign?</i>
ICH	Yes. Differing yield ranges [ICH Q7, 8.14] may be described and justified in the manufacturing procedure/master batch record explaining the ranges [ICH Q7, 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.
APIC	<p>For a known consistent process a yield variation is a potential indication that a process is not performing to expectations. Therefore investigation of variations in yields at defined process steps is intended not only to control variations in production efficiency but also to optimize process consistency and assist in assuring consistent product quality.</p> <p>The expected yield may be defined at designated steps for example key intermediates, the final step of synthesis of the API.</p> <p>It will be easier to calculate the yield of dried products. When wet products or crude liquids are involved, it may be necessary to calculate the yield after analysis and determination of the percentage of expected product.</p> <p>In some cases there could be significant batch to batch variations in yield due to different quantities of product remaining in enclosed equipment such as Milling/sieving, filtration or drying equipment. In these cases monitoring of yield trends or averages over a range of batches may be more appropriate.</p> <p>Yield definition may also not be practicable in purification steps, continuous production processes or processes with multiple recycle streams (e.g. mother liquors). These processes instead may be assessed for example on a weekly or monthly basis.</p> <p>The important point is that companies should evaluate and document the likely yield expectancy and variability and decide what is the expected yield and the likely impact on quality.</p> <p>Once again there are advantages in defining critical process steps to ensure that the yield investigations are focussed on the steps likely to have an impact on product quality.</p>
2	<i>What is meant by ‘appropriate specifications (of each batch) prior to blending’ [ICH Q7, 8.41]?</i>
ICH	As a principle, no batches with Out of Specification (OOS) results should be blended [ICH Q7, 8.41]. Blending is defined in [ICH Q7, 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.
APIC	Appropriate specifications is translated by APIC as filed release specifications

9 Packaging and Identification Labelling of APIs and Intermediates

No Q&A.

10 Storage and Distribution

1	<i>What is meant by ‘APIs and intermediates can be transferred under quarantine to another unit under the company’s control when...’ and is this applicable to contract manufacturers?</i>
ICH	<p>[ICH Q7, 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’.</p> <p>The second sentence in [ICH Q7, 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, different</p>

	<p>site (within the same company), or a contract manufacturer (see final paragraph below).</p> <p>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, 2.22].</p> <p>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 the need to expedite the shipping and the material management system in place to prevent use of the material before full release. Examples of circumstances where transfer under quarantine may be needed include extraordinary supply chain requirement(s) (e.g., short shelf-life), and materials with a lengthy timeframe for required test(s) (e.g., some microbiological tests, etc.).</p> <p>With appropriate oversight as described in [ICH Q10 2.7], including a written agreement as described in [ICH Q7, 16.12], and appropriate ongoing controls, a contract manufacturer may be considered a 'unit under the company's control'. There is a joint responsibility by 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.</p>
APIC	<p>The process of transfer under quarantine should be proceduralised. Quality unit of both sites need to approve the shipment under quarantine and the receiving site cannot use the material before a CoA of the batch in scope is issued.</p> <p>Before shipment under quarantine the manufacturing batch record should be reviewed and approved by the quality unit</p> <p>The final responsibility in the EU is the QP of the MAH</p>

11 Laboratory Controls

1	<i>What is expected in terms of impurities for APIs extracted from herbal or animal tissue origin [ICH Q7, 11.2]?</i>
ICH	<p>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.</p> <p>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.</p> <p>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, 11.21; ICH Q9; ICH Q11].</p>
APIC	If pesticides, mycotoxins, viruses, herbicides, elemental impurities are expected to be present from the source, the risk assessment should cover adequate removal and/or inactivation of the contaminant in downstream processes.
2	<i>In cases where an API test method is changed, which method should be used for stability studies already in progress?</i>

ICH	<p>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, 11.51].</p> <p>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 post-approval changes [ICH Q7, 13.11].</p>
APIC	<p>Parallel testing with both methods can be applied until regulatory approval of the change is received.</p> <p>An equivalence study and report should be established to support the change</p>
3	<p><i>When is it acceptable for an API manufacturer to extend an API retest date [ICH Q7, 11.6]?</i></p>
ICH	<p>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.</p> <p>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.</p>
APIC	<p>The use of a retest date is recommended, this will allow using the API after this date, provided it complies with the specifications. See definition of Retest date.</p> <p>The decision to use a specific API batch with an extended retest period is the responsibility of the Manufacturing Authorization holder.</p> <p>Multiple retesting to extend the API retest date of a specific batch is acceptable and should be proceduralised.</p> <p>The time between testing and use should be limited and justified.</p> <p>Points to consider for extending the retest period of a specific API batch.</p> <ul style="list-style-type: none"> - <i>historical long term stability information</i> - <i>batch testing (retest versus QC release) stored under correct storage and packaging conditions</i> - <i>storage conditions of the batch</i> - <i>validated stability indicating analytical test method</i> <p><i>Material with an expiry date assigned cannot be retested to extend the shelf life.</i></p>
4	<p><i>What is meant by ‘completely distributed’ in [ICH Q7, 11.71], which indicates reserve/retention samples should be retained for 3 years after the batch is completely distributed by the manufacturer?</i></p>
ICH	<p>‘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 applies to all parties that physically process or repackage the API [ICH Q7, 20 – see Glossary for definition of ‘manufacture’].</p> <p>The intent of ICH Q7 is to retain samples 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 was never</p>

	intended that the reserve sample be destroyed before the 5 year retest date was reached.
APIC	It is good industry practice to consider retaining reserve/retention samples for the period of time the drug product(s) in which the API was used may be available on the market. The storage time for reserve/retention samples should be justified and proceduralised.
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, 11.72]?
ICH	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, etc.). Therefore, reserve/retention samples may be stored in packaging (and conditions) that better preserve the original state of the API.
APIC	Self-explanatory

12 Validation

1	Is the lifecycle approach to process validation acceptable for APIs under ICH Q7?
ICH	Yes, ICH Q7 does not preclude the lifecycle approach [ICH Q7, 12.10, ICH Q10, ICH Q11].
APIC	After the original validation (based on a pre-defined and justified number of validation batches) the validation status should be continuously monitored according to Continuous Process Verification (CPV) principles The validation process should be proceduralised
2	Can the range of a process parameter be expanded based only on a process deviation(s)?
ICH	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, 2.16, 12.11, 13.13].
APIC	Process parameter expansion should be supported by Change Control to assure accurate review by all involved departments
3	Would additional process validation studies be needed to support a change in the source of an API starting material?
ICH	Any change in the API starting material should be assessed for impact on the API manufacturing process and the resulting API quality [ICH Q7, 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, 12.1, 13.13].
APIC	A risk assessment should be made to evaluate the depth of validation/verification needed and as specified in the company's supplier qualification procedure. APIC guide on supplier qualification: http://apic.cefic.org/pub/GuidelineSupplierQualification_200912_final.pdf
4	Is a retrospective approach to validation still acceptable?

ICH	<p>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, 12.44].</p> <p>If regulatory discussions redefine a step as critical, which had previously been considered non-critical, a protocol describing retrospective analysis of data together with the commitment for concurrent or prospective validation may be an option.</p> <p>Regardless of the type of validation, the quality system should confirm the ongoing robustness of the process (e.g., product quality review).</p>
APIC	<p>APIC advises to perform a prospective approach taken into account previous batches through statistical evaluation</p> <p>Retrospective validation requires a protocol that covers in detail the acceptance criteria and batch information that will form the basis for validation.</p> <p>Batches that fail to meet specification or are out of trend need to be discussed.</p> <p>The number of batches chosen should be statistically based. The "general rule" from the above judgement is that between 20-30 batches is required, but a firm can depart from this number provided it can support any such departure with statistical or other evidence that supports validation.</p>

13 Change Control

3	<p>Who is responsible for notifying the drug product manufacturer about relevant changes in API manufacturing?</p>
ICH	<p>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, 13.17, 17.60].</p>
APIC	<p>The need to communicate "relevant" changes to the DP manufacturers should be established in the Quality Agreements along the full supply chain. The definition of "relevant changes" should be explained in the quality agreement</p>

14 Rejection and Reuse of Materials

1	<p>Should rejected materials be stored under physical and secure segregation?</p>
ICH	<p>ICH Q7 does not specify a need for physical and secure segregation. Both [ICH Q7, 4.14 and 10.11] 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, 7.44, 10.11, 14.1].</p>
APIC	<p>See 14.1 in the "How to Do" document Non-conforming batches are not necessarily to be destroyed. APIC advocates to use the term "Rejected" only after the disposition decision states "to be destroyed".</p>
2	<p>Does the definition of expiry date in ICH Q7 preclude the rework or reprocess of an expired API?</p>

ICH	<p>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.</p> <p>It may be acceptable to reprocess [ICH Q7, 14.2] or rework [ICH Q7, 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.</p>
APIC	self explaining
3	<i>Is validation expected for the recovery of material from mother liquor?</i>
ICH	<p>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, 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, 12.11, 12.12, 14.41, 14.43, 20 – see Glossary for definitions of ‘critical’, ‘materials’, ‘mother liquor’, and ‘validation’].</p>
APIC	self explaining

15 Complaints and Recalls

1	<i>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?</i>
ICH	<p>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., non-conformance, deviations, etc.) [ICH Q7, 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.</p>
APIC	self explaining
2	<i>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’?</i>
ICH	<p>No, provided that no portion of the batch left direct control of the company for sale or use. It must be clearly visible in the API site’s Quality System as a return triggered by the API manufacturing site so this is clear in quality system trend reporting and in the Product Quality Review [ICH Q7, 2.50, 15.13, and 15.14].</p>
APIC	self explaining

16 Contract Manufacturers (including Laboratories)

1	<i>Does ICH Q7 preclude a contract manufacturer’s independent quality unit from performing the main responsibilities as described in [ICH Q7, 2.22]?</i>
ICH	<p>No. The original intent of section 2.2 was to distinguish the main responsibilities (e.g., batch record review, review of non-conformances and investigations, sampling, testing, release or rejection of intermediate or API, etc.) of the independent quality unit from other departments within a company.</p> <p>Contract manufacturers are expected to have an independent quality unit that meet the responsibilities defined in [ICH Q7, 2.2] for all activities performed.</p> <p>Given the potential complexity of outsourcing contract manufacturing arrangements, GMP responsibilities should be clearly defined between both parties in detail in a</p>

	written agreement [ICH Q7, 16.12]. However, the overall responsibility for API quality must not be delegated.
APIC	APIC Guide: http://apic.cefic.org/pub/GuidelineSupplierQualification_ContractLabs10Jan2012.docx http://apic.cefic.org/pub/QualityAgreementGuideline_final_200912_clean.pdf self explaining
2	Which outsourced activities are covered by ICH Q7?
ICH	In the context of ICH Q7, contract manufacturing is the outsourced activity. The term 'outsourced activities', as defined and described in [ICH Q10, 2.7, Glossary], aligns with the description of 'contract manufacturer' in [ICH Q7, 16]. ICH Q7 defines 'manufacture' as 'all operations of receipt of materials, production, packaging, repackaging, labelling, relabeling, quality control, release, storage, and distribution of APIs and related controls.' 'Related controls' include any activities or services necessary to support production (e.g., maintenance, calibration, etc.). 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.
APIC	self explaining
3	What is meant by 'where subcontracting is allowed' [ICH Q7, 16.14]?
ICH	Subcontracting as used in [ICH Q7, 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, 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, 16.14].
APIC	Subcontracting requirements should be covered in the quality agreement.

17 Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

1	What does ICH Q7 mean by 'Agents, brokers, traders, distributors, repackers, or relabellers'?
ICH	Regardless of what they are referred to 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, 17.1].
APIC	self explaining
2	Could a distributor of an API engage a contract manufacturer for production steps?
ICH	No. If a distributor [ICH Q7, 17.1] of an API contracts out production steps (e.g., drying, micronisation, milling, or sieving), then the distributor becomes a manufacturer and is subject to the entirety of ICH Q7. This includes, but is not limited to, appropriate written agreements as stated in [ICH Q7, 16.12] defining responsibilities of each party. In addition, these contracted production steps must be described in registration documents, applications, or equivalent as per regional requirements.
APIC	self explaining
3	Is it acceptable to replace the original label, which contains the information of the original manufacturer?

ICH	Any relabeling operations are considered manufacturing by definition [ICH Q7, 20] and should be performed under appropriate GMP controls [ICH Q7, 17.40]. With appropriate justification, manufacturers including repackagers and relabellers may replace the original label. The new label should contain information as per [ICH Q7, 9.42, 9.43]. However, distributors should not remove an original label, but only add additional labels. Information about the original manufacturer must be provided to the customers [ICH Q7, 17.61]. Overall, the traceability of the supply chain needs to be maintained [ICH Q7, 17.2].
APIC	self explaining
4	<i>Who is considered to be the original manufacturer of the API for purposes of the Certificate of Analysis (CoA)?</i>
ICH	The CoA should document the original manufacturer to support traceability throughout the supply chain [ICH Q7, 11.4, 17.6]. The original manufacturer would be the facility where the final purified API/intermediate is produced. Further physical processing (e.g., drying, micronisation, 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, 17.20].
APIC	self explaining

18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

1	<i>Does ICH Q7 expect validation for viral removal/viral inactivation steps for biological/biotechnological products?</i>
ICH	Yes. According to [ICH Q7, 18.51], viral inactivation/removal steps are considered critical for some processes (e.g., cell lines of human and animal origin [ICH Q5A, 1]. Parameters for validation should be established in accordance with [ICH Q5A, Q5D and Q6B]. Due to the potential for contamination [ICH Q5A, 2.B], viral inactivation studies should be performed in a separate and typically smaller laboratory facility [ICH Q11, 7.2] and not in a clinical or commercial manufacturing facility.
APIC	self explaining
2	<i>Do the sections [ICH Q7, 18.14, 18.2] apply to classical fermentation and biotechnology?</i>
ICH	For 'classical fermentation', the text from [ICH Q7, 18.14] ' <i>...this guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing</i> ' refers to 'classical fermentation' and not to the 'biotechnology fermentation/cell culture'. Although the entire ICH Q7 guideline does not apply prior to the introduction of cells into the classical fermentation process, as shown in Table 1 of [ICH Q7, 1.3], an appropriate level of GMP controls suitable for cell banks should be established. For 'biotechnology fermentation/cell culture' the section [ICH Q7, 18.2] on ' <i>Cell Bank Maintenance and Record Keeping</i> ' applies specifically to biotechnology fermentation/cell culture because ICH Q7 starts with the maintenance of the working cell bank [ICH Q7, 1.3, Table 1]. Although for biotech products the entire ICH Q7 guideline 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].
APIC	self explaining

19 APIs for Use in Clinical Trials

1	<i>Is it permitted to use the same equipment to manufacture materials to be used in pre-clinical and clinical trials?</i>
ICH	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, 19.3].
APIC	https://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf Glossary
2	<i>Are the terms 'deviation' and 'non-conformance' synonyms?</i>
ICH	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. 'Non-conformance' refers to a status as a result of a failure of the material to meet specifications or appropriately established standards that impacts the quality of the material [ICH Q7, 2.50, 14.30, 20].
APIC	self explaining

20 References

The documents are published at www.ich.org .

- ICH E2E Pharmacovigilance Planning, Nov. 2004.
- ICH Q1A(R2) Stability testing of new drug substance and products, Feb. 2003.
- ICH Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin, Sept. 1999.
- ICH Q5B Quality of biotechnological products: Analysis of the construct in cells used for the production of r-DNA derived protein products, Nov. 2005
- ICH Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, July 1997.
- ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, Mar. 1999.
- ICH Q7 Good Manufacturing Practice of APIs, Nov. 2000.
- ICH Q8(R2) Pharmaceutical Development, Aug. 2009; Part I: 'Pharmaceutical Development', Nov. 2006; Part II: 'Annex to Pharmaceutical Development', Nov. 2008.
- ICH Q9 Quality Risk Management, Nov. 2005; and the ICH Q9 Briefing pack.
- ICH Q10 Pharmaceutical Quality Systems, Jun. 2008.
- ICH Q-IWG Training Programme for ICH Q8/Q9/Q10, Nov. 2010.
- ICH Q11 Development and Manufacturing of APIs, May 2012.

21 Annex: Q&As linked to the respective sections 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 Labelling 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 Relabellers	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																			
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5		2.50																			Q10
6		2.50 2.51																			Q9
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4. Buildings and Facilities – Containment																					
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5. Process Equipment – Cleaning																					
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6. Documents and Records																					
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9. Packaging and Identification Labelling of APIs and Intermediates																					
10. Storage and Distribution																					

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 Labelling 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 Relabellers	18: Specific Guidance for APIs manufactured by Cell Culture/Fermentation	19: APIs for Use in Clinical Trials	20: Glossary	Other ICH Guidelines
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