ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

APIC Active Pharmaceutical Ingredients Committee

cefic

GMPs for APIs:

"How to do" Document

Interpretation of the ICH Q7 Guide

Version 8
(Update August 2015)

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(Revised chapters in this Version are highlighted in blue)

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 year's 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.

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 An APIC combined Regulatory/Quality work group is implemented to bring this guidance in line with current expectations (for instance ICH Q11). The “how to do” document will be updated accordingly after approval by the APIC Excom. In the interim this section has been deleted as the guidance was no longer compatible with current regulatory or industry thinking.

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. Whether electronic or manual systems and records that 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 and inspection readiness should be pointed out, which directly ensures benefit to the patient. To implement a QMS integrating GMP issues, please refer to the Guide "Quality Management System for Active Pharmaceutical Ingredients Manufacturers", APIC, September 2005.	
2.10	Company management should empower Quality responsibility to the appropriate organisational functions to apply the Quality policy and procedures. Assignment of clear Roles & Responsibilities for duties and decisions is the basic rule and can be achieved by e.g. process descriptions including principles of RASCI (Responsible, Accountable, Consulted, Supportive and Informed) and decision trees. Delegated responsibilities should be trained, documented and periodically re-trained.
2.11	A clearly defined QMS (as defined e.g. in the APIC Guide (see above), ICH Q10 and ISO 9001: 2000 or later) integrating API GMP requirements, should be documented, implemented and described e.g. in the Quality Policy.
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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 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. 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.
2.14	Release of raw materials and intermediates meeting the specifications (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. 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.

2.15	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. Recording in non-traceable documents like a blank sheet of paper (re-writing afterwards into traceable documents) is not acceptable. Electronic documents and recording requires appropriate validation of the systems used (see chapter 5.4 and 6.1).
2.16	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.
2.17	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).
2.18	As an example a regular report system should be made available to senior management by the QU informing of acute occurrences (quality related complaints, critical deviations, recalls, etc.). Senior management should review and agree any recommendations and ensure that appropriate resources are made available. Quality (or: key) performance indicators could be installed to evaluate continuous quality improvement of the department.

2.2 Responsibilities of the Quality Unit(s)

2.20a	QU duties may be delegated 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).
2.20b	The Quality Compliance Unit will be responsible for implementing a Quality Risk Management (QRM based on ICH Q9) - QRM is applicable during design, development, manufacturing, packaging, testing, 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 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. A Procedure must be in place with the intention to assure the consistency of a Quality Risk management application including: 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. 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 **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	Although in this section it is stated "…should not be delegated" it is likely that companies will face problems during inspections if they come up with alternatives; this "should" has to be interpreted as "must". Only 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) 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 ICH Q7 chapter 11.60), 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 filed specifications of Raw Materials and Intermediates, documented periodical review by the quality unit for delegated release to production should occur (ref. 2.5).

2.3 Responsibility for Production Activities

2.30	An additional advice for the assignment of quality related duties to Production and other functions / departments can be found in "EudraLex, The Rules Governing Medic-

	inal Products in the European Union, Volume 4: EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use."

2.4 Internal Audits (Self-Inspections)

2.40	SeeApic/Ceficauditguideline: http://apic.cefic.org/pub/Auditing/Auditing%20Guide%20update%20Sep%202008final.pdfInternal 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. The evaluation should be made by trained auditors, experienced in auditing skills and recruited from various departments of the company, if possible. Quality Inspection Teams (QIT) 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 should always be represented in a team, but not always taking the lead for not being accused to be the "policeman". The QU should be responsible for co-ordinating activities such as follows: • pre-audit meetings for the QIT (brain storming) • identifying major areas of concern and preparation of questions (questionnaire) • 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 QIT • starting the (internal) audit and summarising the findings in a close out meeting • issuing the audit report, on the basis of the close out meeting • propose corrective measures or improvements to management • schedule (propose) a re-audit in case of major findings • follow-up. Other members of the QIT could be involved in asking and taking extensive notes. The whole auditing process should be clearly defined and the following standard documents should be considered to be available in a generic layout form: • Definition of auditing process, system or product • Covering Letter • Report Form • Audit Team Evaluation Form • Follow-up Report • Training Programme The frequency of the self-inspections should be based on risk (a formal risk assessment may not be necessary) as well as the compliance status of the area to be audited. It may vary from half a year to three years, and the rationale behind the frequency should be documented. The compliance status of the area to be audited and may vary from half a year to three years. All participants in the QIT 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. If possible internal audits should not take more than to 3 - 4 hours. Remember to include at a minimum twice the time for preparing and writing the audit reports.

	It is important to define deadlines for issuing (recommendation: 2 weeks) and finalising (recommendation: 4 weeks) the report and for the first follow-up meeting. The internal Audit Report as well as the Follow-up Report should be kept confidential and should not be shown to external personnel, especially inspectors from authorities. 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. 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.
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2.5 Product Quality Review

2.50	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. 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. To ensure that key data is reviewed it is essential for each production process to identify the critical in process controls and critical API (or relevant intermediate) test results. These would normally be the critical API test results which may be used to indicate the consistency of the process or to assess potential deviations in the quality of the API itself. In addition the critical reaction parameters should be evaluated. 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. In nearly all cases specification limits for the critical test results are in place. Therefore the first evaluation would consider the failure frequency to meet such limits. In addition any trends in data should be evaluated across the batches produced during the review period. Appropriate statistical tools may be used to assess process capability when data from a large number of batches is being reviewed. An example of these statistical tools can be the establishment of key performance indicators. 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. 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. Common causes for batch failures and recurring deviations are (this list should not be regarded as complete): • 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. 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 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. 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. The status of quality related returns, complaints or recalls should evaluate the adequacy of corrective actions and any trends which require further investigation.
2.51	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 revalidation where significant changes or alterations in the trends of the key quality data indicate this is necessary. 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.

Chapter 3 Personnel

General Remarks
The environment 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.

3.1 Personnel qualifications

3.10	For the first time there is a requirement that everyone involved in the manufacture of intermediates and APIs needs education (schooling) appropriate to the task to be performed. This education needs to be supplemented by training and/or experience in the particular task to be performed.
3.11	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. This can be accomplished either in a generic way for a group of personnel e.g. warehouse personnel or operators in chemical production. 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 description. 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. 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. Job descriptions or function descriptions should identify the main purpose, role dimensions, outputs/responsibilities, reporting details and required competencies. These should be reviewed regularly.
3.12	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.) GMP refresher training should be conducted at least annually. Training in particular operations that the employee performs might be carried through under supervision by a person qualified by education, training and experience. Before a person is allowed to sign a particular operation in the batch record he should be qualified by education or should have received appropriate training. GMP training should be scheduled regularly and conducted according to a plan. Training records should indicate the • names of the people trained, • subject of training in keywords • date of training • name of trainer If procedures are revised or newly released the need for appropriate training should be assessed. Effectiveness of training can be verified by direct (e.g. testing, questionnaire) and/or indirect means, e.g. individual observations, periodical assessment (usually annual) interview with supervisor or Internal Audits. 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,.

3.2 Personnel Hygiene

The intention of this chapter is to protect personnel as well as products. The type of protection garments for each chemical operation may be given in the production or safety instructions. These instructions should be followed and checked.

Personal hygiene should also be practised by maintenance staff, contractors, visitors, consultants, and inspectors as appropriate.

People not trained in the departmental Hygiene and gowning procedures can only enter the department if accompanied by an authorized, trained person. The decision on the impact of a person suffering from an infectious disease on the job and products can be decided in a combined decision between the supervisor and the occupation health practitioner.

3.21	1) If gowning instructions are required to protect the API from contamination from the environment these instructions must be written in a controlled document. 2) For asep-

	tic sterile API manufacturing the Personnel requirements are described in the Annex 1 of the Eudralex vol. 4

3.3 Consultants

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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 tremendous increase of GMP understanding and principles which has been taken place in the API producing chemical industry during the past years. The ISPE Baseline Guide for New Facilities Volume 1 Bulk Pharmaceutical Chemicals (June 1996) is well known as a useful reference. It should also be noted that all literature references made in this 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 is a suitable method to identify additional measures (design or organisational) to bring "old" plants into compliance and also appropriate retrospective qualification is recommended.

A 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 requirements as required by the he finished product.

-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	An increase of product protection is expected from early steps to the final API, especially for areas where open handling of the API without further purification is performed (e.g. drying, milling, weighing and packaging etc.). 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. The risk assessment should consider the following at a minimum to identify where the API is at risk from contamination: 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 excipient quality, and f) Presence of airborne contaminants, especially highly sensitizing or toxic substances. Where existing controls to minimize the risks of API contamination are not considered effective then additional measures should be documented and implemented. The ISPE 2008 white paper on the briefly open concept is advised. In principle there are two options to achieve this goal: Open systems (products are handled temporarily in the open environment) or closed systems. 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. For long term exposure a suitably installed (e.g. according to ISPE Baseline Guide "Commissioning and Qualification") and well maintained air handling system could ensure the necessary protection.
	Some other precautions include: – Spatial separation – protecting equipment during open product handling (e.g. covering, glove boxes, isolators etc.) – Design of piping (should not be located directly above open manholes, discharging devices etc. unless appropriate protecting measures are in place – Filtering of process gases and solvents 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	This specific requirement is of particular importance in multipurpose plants with variable equipment.
4.12	Reactors, fermenters, crystallisers, distillation columns, tank farms, storage containers or other closed equipment may be located outdoors, provided there is no need to pro-

	tect from weather influences. Also not permanently installed equipment (e.g. bulk containers, etc.) may be stored outside, if adequately protected.
4.13	Sometimes (especially in "old" plants) crossing of material or personnel flow cannot be avoided. In this instances additional organisational measures (SOP´s) should be implemented to ensure prevention from mix-ups and contamination.
4.14	Other control systems can be computerised material management systems. Quarantined and released materials (APIs, raw materials, intermediates, could be stored in the same area (but no mix-ups on pallets etc.), provided their status is clearly indicated and/or traceable (labels, computer status) and procedures are in place to avoid unauthorised use. For safety reasons separate storage facilities may be required for classes of materials with hazardous and /or unstable chemical or physical attributes. Separate production areas are required for certain materials (see 4.4)
4.15	-
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	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 or nitrogen blanketing, or in contact to the inner surface of equipment. When using compressed air with direct product contact it is recommended to use oil free systems. 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.
4.21	Appropriate only if open systems are used (reference to 4.12). If open systems are used the "ISPE Baseline Guide for New Facilities Volume 1 Bulk Pharmaceutical Chemicals (June 1996)" provides useful information (reference to 4.1). A risk based design is appropriate in an API manufacturing site with increasing environmental protection from Stating Material to final API taken into account the final API dosage form.
4.22	Appropriate measures may be e.g.: • selection of suitable filters (and appropriate change of them) • mixing of returned air with fresh filtered air • clean up time (e.g. verified by particle measurements) on product change; including cleaning or changing of filters. • If air is humidified during the recirculation process tha water quality must be justified (Example when micro specs to the API are required and for low bioburden API's).
4.23	Although it is required that permanently installed pipework should be identified, 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). 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 swannecks. Draining valves should be installed at the lowest points. During design, methods of cleaning of pipework should be considered.
4.24	If needed drains should be sanitized at regular intervals avoiding microbial growth. Such sanitization may be simply conducted through use of an appropriate cleaning agent

4.3 Water

4.30	Develop a rationale as to what water quality is sufficient and/or which measures may need to be taken to ensure API quality. Suitability depends on the stage in manufacture, intended route of administration or the nature of the API. Evidence should be available that the water used does not negatively affect the product quality.
4.31	Water quality should be monitored by the supplier and the results be reported to the API manufacturer on a routine basis. Additional in-house testing and monitoring should be considered by the manufacturer according to a predefined and approved plan (including point of use testing, sampling frequency) against predefined specifications that ensure a safe and sound quality of the API (usually meeting guidelines for potable water, unless otherwise justified). Potable water may be even more suitable for use than treated (softened) water due to measures taken to limit microbial growth.
4.32	It is the responsibility of the manufacturer to define the specifications of the water quality by himself to assure the quality of the API. The assessment should take into account the intended use and the final purification step(s) of the API. The CPMP and CVMP "Note for Guidance on Quality of Water for Pharmaceutical Use" should also be considered during this assessment (if the API or the resulting Drug Product is distributed within the EU).
4.33	Validation principles (chapter 12) and change control (chapter 13) need to be applied.
4.34	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 recommended.

4.4 Containment

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4.41	-
4.42	For certain APIs (see 4.40 and 4.41) it may be appropriate to use dedicated or dis-

	posable 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.
4.43	The comments made on 4.14 should be applied however the storage of closed containers in a common area can be accepted. For non highly toxic non pharmaceutical materials for example pesticides and herbicides you may refer to local authorities for local requirements

4.5 Lighting

4.50	Should comply with National regulations (e.g. Health & Safety).

4.6 Sewage and Refuse

4.60	Disposal has to be performed according to National law. In order to prevent misuse it may be necessary to ensure physical destruction, e.g. incineration of certain APIs, e.g. narcotics.

4.7 Sanitation and Maintenance

4.70	It has to be pointed out that there is a significant difference between a finished dose 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 a 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. Additional guidance may be found in the ISPE Baseline Guide Volume 1, "Bulk Pharmaceutical Chemicals" (June 1996) Defined areas for the storage of temporarily used equipment and its status, (cleaned, identified and protected from the environment), should be available.
4.71	Cleaning of accidental spills and also routine cleaning programmes should be defined. External contractors are often used for sanitation and facility cleaning activities. They should be trained in GMP and their responsibilities defined in a contract (see chapter 16).
4.72	It is not recommended to use these toxic materials in areas where open product handling occurs.

Chapter 5 Process Equipment

5.1 Design and Construction

5.10	The ISPE baseline guide volume 5 "Commissioning and Qualification" gives a very pragmatic system to ensure that systems are "fit for purpose". 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.
5.11	Materials of construction 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.
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. 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, PQ). An example of this may be a temperature probe that can monitor temperatures over a range –20 to 150 ^{o}C but that can also be tuned to enable a reaction temperature of just +/-2 ^{o}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.
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 content and potential quality impact. TheFDAwebpage: 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. 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 that needs regular attention to prevent failure.
5.21 to 5.26	See the APIC Documents "Cleaning Validation in Active Pharmaceutical Plants – Policy, 1999" and "Cleaning Validation in Active Pharmaceutical Plants – Guidance" for practical advice on this subject. (http://apic.cefic.org, "publications").

5.3 Calibration

5.30	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. Classifying instruments as: critical **GMP**= CPP (critical process parameter)or CQA (critical quality attributes) controlling equipment, **GMP** = direct quality impacting, **GEP** = indirect or non-quality impacting. 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 competent to undertake the calibration to the appropriate standards.
5.31	This applies more specifically to critical instruments.
5.32	As per document retention requirements in section 6.
5.33	A very good approach is to calibrate prior to start up 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.
5.34	A procedure should exist to ensure that instruments not meeting calibration criteria are not be used. It is for this reason that tolerance ranges and calibrations should be appropriately selected for the process to ensure that non-impacting failures of calibration criteria are not routinely observed.
5.35	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.

5.4 Computerized Systems

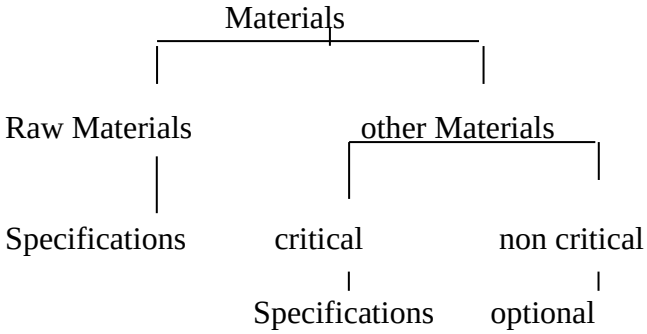
Computerised systems have a very high profile and require an extremely thorough validation approach. It is an area of high inspector interest especially for suppliers of the US market. Reference: Computer validation guideline by APIC is available (http://apic.cefic.org/publications/publications.html) and this provides some pragmatic guidance in an area which often involves large amounts of paperwork with too often distressingly low value. Another reference is GAMP 4 (issued by ISPE; http://www.ispe.org)	
5.40	The validation assessment system defined by the ISPE is also a very useful analysis technique to use so that resources and effort are appropriately targeted on critical systems.
5.41	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.
5.42	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.
5.43	Basic security measures such as access control 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 the 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.
5.44	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.
5.45	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.
5.46	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
5.47	Change control should be appropriate to the criticality of the system. GEP systems should not require quality review.
5.48	For critical systems a back up 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.
5.49	Digital readouts etc. can be documented manually or by use of chart recorders.

Chapter 6 Documentation and Records

6.1 Documentation System and Specification

6.10	–
6.11	Regarding revision of documents, the company should define e.g. in a SOP when and how documents are revised. Issuing a new table listing all existing documents/SOPS after a defined period of time (not necessarily 2 years) is acceptable. A useful way to demonstrate that documents have been reviewed and revised is to prepare a report on periodic basis that lists all the documents that have been changed and reissued. 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.
6.12	Suggested minimum retention periods: - general production, analytical, control and distribution records 7 years * - clinical batches for an IND or NDA (see also chapter 19) LC + 1 year - batches for bioequivalence testing LC + 1 year - product development reports LC + 1 year - development and validation reports of analytical test procedures LC + 1 year - process validation reports LC + 1 year - equipment IQ, OQ and PQ reports LC + 1 year - supporting systems (e.g. utilities, computerised systems) LC + 1 year - training records 7 years (for clinical trials and demonstration batches LC + 1 year should be considered) **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 stadium "status" of not in use. * after the date of the record
6.13	**(1) There is a contradiction regarding retention periods of i.e.** *All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with test dates, records should be retained for at least 3 years after the batch is completely distributed.* **as described in section 6.13 of the ICH Q7 guideline compared to the respective HOW TO DO interpretation / advice summarized section 6.12** *general production, analytical, control and distribution records: 7 years* (* after the date of the record).*
6.14	No pencil, no white out and no crossing out and no obliteration of an original entry that is subsequently corrected.
6.15	–
6.16	–

6.17



Item	**Type of Specification**
API Starting Materials,	Internal specification mandatory. More details may be needed compared to RM. Pharmacopoeia requirements grade materials are not needed. unless necessary to control the quality of the final API
Raw materials	Internal specification mandatory. Pharmacopoeia grade materials are requirements not needed unless necessary to control the quality of the final API
Intermediates	Internal specification optional. Pharmacopoeia grade materials are requirements not needed unless necessary to control the quality of the final API
APIs	Pharmacopoeia mandatory. For non-compendial APIs refer to Q6a. Additional internal specifications optional if stipulated by customers.
Labelling	Pharmacopoeia and internal specifications mandatory concerning text of labels. Material specification optional.
Packing material	Printing see labelling. Material specification mandatory.
Process aids including utilities (product contact materials)	If such materials are critical, the use of internal or public specifications (e.g. technical standards like ISO, EN etc.) is advisory.
IPC	In order to avoid the necessity of doing OOS-Investigations on deviating in-process controls, ranges need to be established for every IPC test identified as a critical IPC. .

6.18 –

6.2 Equipment Cleaning and Use Record

6.20	It is recommended to use a log system (but separate records would also be acceptable (different documents) for the chronological record in order to see: - for which purpose and batch the equipment has been used - from whom and how (cleaning method used) it has been cleaned (when appropriate) - any maintenance that was done referring to who did it, what and how it was done (a reference in the batch record should be made, if maintenance was performed during production). - the status before and after maintenance, even when the equipment was found to be o.k. This requirement is valid for major equipment only (ref. 6.52). It is important to describe the exact type of repair of the equipment in the record. Status of equipment should be recorded and checked. Status of cleaning and maintenance should be recorded and checked, preferable in a log. Cleaning and maintenance may be documented in a database (electronic records) which then should comply with section 6.10 and 6.18.
6.21	A plant or unit log instead of individual equipment records should also be applicable if the equipment is firmly incorporated into a plant or unit (installed and piped for permanent use) even if this plant/unit is not dedicated but used for production of different APIs in campaigns. 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 double signed. The review of the batch record will then be easier. If the cleaning and maintenance records are not part of the batch record, a reference to the appropriate documentation or database should be placed in the batch record. The objective of this record keeping is to trace what particular equipment was used in manufacturing (see glossary of Q7) a particular batch and what status it had at the time of usage.

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 suppliers production records and trace forward until the API-batch delivered to individual customers in case of any failure occurring in the supply chain. The responsibilities for a final decision regarding rejected raw materials etc. should be defined in a procedure.
6.31	The approved master of a label need not to be a label itself but may consist of a approved set of relevant data used by or sent to a label printer. A 0-copy of the label may be filled together with the batch record to proof compliance with such master.

6.4 Master Production Instructions (Master Production and Control Records)

6.40	Review and signing by two people is sufficient but not restricted to that number. . One should be in the Quality unit. The review has to be performed by the people/functions appropriate for this task. This may involve R&D, QC, Production, engineering and probably also regulatory affairs as well as SHE (safety, health, environment) departments.
6.41	It is possible to use, at different production locations, different Master Production Records derived from the same basic receipt

6.5 Batch Production Records (Batch Production and Control Records)

6.50	The third sentence may refer to the situation that a company, e.g. for business reasons, has the possibility to manufacture a product in different batch sizes, always using the same basic recipe. This recipe then is the current master production instruction.
6.51	-
6.52	• 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 • 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. •
6.53	An investigation has to be set up at every critical deviation when the origin of the deviation or when the impact on the product quality isn't known. A SOP on investigations of critical process deviations should define what is to be understood by critical. Compare other (related) batches with the same deviation. Use of the principles in ICH Q9 (Quality risk assessment) is a very useful way to classify critical deviations

6.6 Laboratory Control Records

6.60	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. 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. 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 can be done on a sheet/record where all results have been summarised

6.61	Modifications of analytical methods should be subject to change control and considered for revalidation prior to introduction.

6.7 Batch Production Record Review

6.70	"Established specifications" can not always be limited to pharmacopoeia specifications, also additional in-house specifications could apply.
6.71	During a batch record review check for • 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 • impact of reported deviations on product quality • compliance with specifications, parameter ranges or acceptance criteria including tighter customer specifications • usage decision
6.72	See comments on 6.71 and 8.15
6.73	–

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 critical raw materials based on good scientific rational and impact on the quality of the API. Suppliers (manufacturers and/or agents if applicable) of critical materials should be evaluated and approved by the quality unit. The evaluation can be based on

- historical experience with the supplier,
- on 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 for example if deviations are observed. Other useful information can include the reputation of

the supplier within the industry and the availability of certificates such as ISO-9000 certificates. The evaluation and approval process should be described in a procedure, taking into account some or all these possibilities. This includes the fact that the name and address of the manufacturer of a critical material must always be known. A change of the source (e.g .manufacturer or supplier) of a critical 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. As long as the material is not released it must be held under quarantine; this can be realised in different ways e.g. separate areas or through a validated computer system. These systems or others may also be used to identify the status of the material.

Incoming stock materials should be released before mixing them with the existing stock. This new stock should get a new lot number.

Non-dedicated tankers should be checked for cleanliness before use to prevent cross-contamination. Ideally, a cleaning certificate should be provided with each supply. If no such certificate can be provided, an audit of the cleaning procedure of the suppliers and/or transport company is recommended.

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

<u>Manufacturing and Supply Process/Homogeneity</u>

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 manufacturers 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, should reduced sampling and testing be considered.

Common industry practice is to use $\sqrt{n}+1$ (where n = number of containers) and is widely accepted in many situations and even though it has no statistical basis it reflects those statistically based. Other examples of sampling plans are British Standard 6001-1, ISO 2859, ANSI/ASQCZ1.4-1993, derivatives of $\sqrt{n}+1$ in WHO document, 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. These scenarios should be justified and documented. Highly hazardous raw materials which are not sampled and tested before release should be evaluated as per ICH Q7 section 7.32

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. 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.

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 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 opening these containers they should be cleaned appropriately.

7.5 Re-evaluation

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Chapter 8 Production and In-Process Controls

8.1 Production Operations

8.10	Weighing or measuring of raw materials (solids and liquids) should follow procedures designed to ensure accuracy and to avoid cross contamination. These may include: • Specified weighing or measuring areas protected from the environment with controlled access. • 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. • Regular checks and records by operational staff that balances are functioning correctly should also be considered.
8.11	Examples of suitable primary container for sub-dividing solids are • a plastic bag for smaller quantities or • plastic bags, liners inside rigid support, or • loading hoppers for quantities of solids. 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.

8.12	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 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 would fulfil the requirement. • "witnessed" = second person checking, not permanently present 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 could be checked at the end of the batch production. 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.
8.13	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 : • 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, ideally on the Master Batch Instructions (see 8.15).
8.14	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. The expected yield may be defined at designated steps for example key intermediates, the final step of synthesis of the API. 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. 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. 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. 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. 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.
8.15	A deviation is defined as a departure from an approved instruction or established standard. The guidelines require that ANY deviation to the defined processing steps in the production records should be documented. 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. It is then the responsibility of the persons reviewing the completed production records (Production) to decide which deviations could be considered critical and require investigation. The Quality Unit should check the deviation records (not the full production/batch records!) The Quality Unit should check the deviations to see the procedure was followed and CRITICAL deviation records for impact on API quality and ensure that critical deviations were investigated (reference 2.22 and 6.72 ICH Q7). A critical deviation is defined as a variation to previously established critical parameters or a significant variation to standard operations which COULD affect the quality of the API or intermediate. Critical deviations should always be investigated and corrective actions identified. Corrective actions should be subject to change control procedures. 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. This review may be done as part of the Product Quality Review. See Section2.5. Examples of deviations are: • Incorrect charging of raw materials • Temperature, pressure, vacuum parameters 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. • Temporary alteration to defined production instructions • In Process Control Limits not achieved. • Alternative production equipment used at short notice. • Extraneous contamination of API and intermediates • Any other unplanned event.
8.16	Defining the process status of equipment is intended to assist the process operators and supervisors to properly control their operations and avoid the miss-use of equipment. In particular the following examples should be well controlled: • The batch number and process in operation • The cleanliness status of equipment

	• Equipment under maintenance, Out of Service or Out of Calibration
8.17	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. 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.

8.2 Time Limits

8.20	Examples of possible deviations of time limits for processing steps are: • 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	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. 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. The retest or shelf life period can be determined by: • 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 Special care should be taken with the storage of wet intermediates, to assess the likelihood of degradation.

8.3 In-process Sampling and Controls

8.30 – 8.31	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 • 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	Sampling is required to be scientifically sound. This is a common sense approach to a

	potentially critical procedure. 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. Sampling procedures are therefore a highly important part of GMP The importance of sample integrity should not be overshadowed by the focus upon the result. Scientific sound sampling procedures should be developed by considering the following issues: • 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). 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. 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. 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 a nice point between sample every container and sample only one ISO 2859 Sampling procedures for inspection by attributes is an alternative reference.
8.35	Sampling tools should be controlled by a cleaning procedure and should be adequately stored when not in use to avoid contamination. 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. 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. In process sample containers should be clean, clearly labelled with product name or code, date, time, batch number, step number, operator name, if relevant. Reference: ISPE Baseline BPC Guide Current version is called "ISPE Baseline Guide: Active Pharmaceutical Ingredients Second Edition June 2007.

8.36	In-process tests that require OOS should be clearly identified/designated and these should be critical tests only.

8.4 Blending Batches of Intermediates or APIs

8.40	–
8.41 – 8.42	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. 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.
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	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. 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. Some of the risks which should be assessed are as follows: Where more than one product is manufactured simultaneously in one production area or building strict procedures should be in force to avoid for example the misuse of raw materials and intermediates during processing operations. • Generally such 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 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, off loading 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 on Bulk Pharmaceutical Engineering Guide 1996**. 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 Pharmaceutical BPC Guide for New Facilities Volume 1 chapter 3** offers detailed guidance on how to assess the risk of cross 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. Also a lot of requirements are established for pre-printed labels or labels that are printed by on site computer and stored. In the API industry most labels are printed on demand, and therefore these requirements are not applicable.	
9.10	Labelling materials: Applicable only for pre-printed labels or labels that are 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	Typically most APIs are stored and shipped in fibre drums with polyethylene liners or polyethylene bags. The inner lining or bag in direct contact with the API should be of food grade plastic (if intended for shipment to the U.S.) or comply with local regulations. The inner packaging should be controlled by the company with respect to identity and traceability.
9.21	Industry practice is to inspect these packaging materials for defects and cleanliness. Sanitising containers does not imply sterilisation. In most instances, sterilisation is not applicable for API packaging materials.
9.22	• For the same product: Visual inspection should be enough, effectiveness of cleaning should have been demonstrated (e.g. by cleaning validation). • For multi-use: Cleaning procedure has to be validated, or at a minimum, depending on the stage of manufacture, analytical verification has to be performed. Remarks: Only applicable if product is in direct contact with the surface of the container, and not if in-liners are used (PE bags etc.)
9.3	For the API industry, computer printed labels are a norm and 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 HTDD 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". 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 re-labelling with customer specific information as part of manufacture / dispensing / shipment is common practice. These activities have to be documented in the batch record or other systems in place, e.g. dispensing records.
9.41	One labelling operation at the same time, only one batch to be labelled (not to be interpretated as stored) on one pallet or in a defined area (specially separated). Also bar-code systems correlating batches to labels could be used to prevent mix-ups.
9.42	–
9.43	If the retest date is extended and mentioned on the label, the label must be replaced to reflect the extended retest date.
9.44	–

9.45	Examination results should be documented as described in 9.44 and not necessarily in the batch record, however the documentation could be attached to the batch record, but also other systems which are retrievable could be used.
9.46	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.

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 are very rarely necessary; they 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. Besides being indicated by stability studies other reasons can result in the need for special storage conditions. Examples are: avoidance of odorous or highly toxicity materials in the proximity of the API and the heat treated wooden pallets policy. 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 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

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>; 2 - Guide IEC 60068 – Environmental Testing - part 1 to 7 from Austrian Institute of Technology 3 - Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances from IMB

	Acceptance criteria for different storage conditions (examples are: controlled room temperature, cold chain, freezers,...) can be found in the EMA directive 2001/83/EC and in the IMB guide to control and monitoring of storage and transportation temperature conditions for medicinal products and active substances with reference IA-G0011-1 from October 05, 2011. The calculation and use of mean kinetic temperature is included. 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
10.11	Acceptable separate storage areas for such activities may solely be marked shelving or floor spaces with the exception of areas for rejected or recalled products in which physical barriers should be utilised to prevent unauthorised use, e.g. locked cages, areas or rooms. Alternative systems may be computerised stock control with restricted access. These do not require separated areas. Physical separation of non-conforming (e.g. returned material) product is necessary separate identified areas should be used. For intermediates the storage conditions are based on product knowledge and development data. For purchased Raw Materials the manufacturer advised storage conditions must be applied.

10.2 Distribution procedures

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 intercontinentally adequate supply chain controls should be in place. For intercontinental 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. For shipments between different sites of the same company a documented risk based approach can be used to justify not applying these standards.	
10.20	Distribution under quarantine is acceptable when under the control of the Quality Unit of manufacturer of the API or intermediate and only for transport to third parties and agreed by the quality units of both parties. Controls might be described in the quality agreement supported by a formal document and formal control system in place at the third party to assure necessary control of the quarantined material For subcontracted activities the formal quality agreement should cover this scenario as recommended in Chapter 16.
10.21	Logistics companies who are contracted to move API should be qualified. A quality agreement should also be in place (or equivalent) which details the key requirements for the safe and effective transportation of the API. Appropriate protective outer pack-

	aging and a reliable shipper 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. 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.
10.22	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.
10.23	Appropriate transport and storage requirements are typically conveyed to the shipper on the bill of lading. If very special storage conditions are required to avoid alteration, it might be necessary to monitor the shipping conditions and to retain records of these conditions.
10.24	Full traceability for all shipments from the manufacturer to its external customer(s) has to be in place. 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 should be the duty of the broker).

Chapter 11 Laboratory Controls

11.1 General Control

11.10	The laboratory facilities at disposal of the Quality Unit can be internal or external: – 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. Whatever the laboratory selected, the responsibilities remains within the Quality Unit of the producer (see 2.22). 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 vibration, …). Separate rooms for different kind of tests (microbiology, chemistry, powder handling, etc.) can be needed.
11.11	The laboratory should have SOPs describing: • Sampling 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. Rounding rules as described in the pharmacopeia should be followed as part of the calculations and assessment to the specification criteria and defined in a SOP. – If analytical results need to be averaged to obtain the final value, the process used for averaging should be described in a SOP. – . 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. Cfr FDA guidance for industry investigation of (OOS) test results for pharmaceutical production (October 2006 – chapter IV.C reporting testing results) • <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)
11.12	Chapter 11.12 is self-explaining.
11.13	When establishing API specifications 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 B) And/or the specifications can be based on the design space using design of experiments when available.
11.14	In order to demonstrate test results are documented at the time of execution. The QC laboratory can use laboratory notebooks (bound notebook pre-numbered) or an equiv-

	alent laboratory notebook (one option is the use of loose sheets pre-numbered, the printing have to be controlled and also the storage as control records). An electronic and validated data collection system can also be used to record the raw data at the time it is produced. Departures from the procedures should be managed according to the deviation SOP.
11.15	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) -MHRA: http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con100182.pdf – OOT results should be investigated and documented as OOS results – Impact on other analyses/tests (results)/batches/products,…. should be considered as part of the OOS/OOT investigation (see 6.53)
11.16	"Use by" dates are appropriate for those analytical reagents and standard solutions where its purity or standardised value can potentially change with the time.. If the supplier provides a "use by" this should be applied, 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. When appropriate, standard solutions can be re-standardised and a new "use by" date can be assigned and documented.
11.17	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. When methods described in an official pharmacopoeia require reference standards, they have to be acquired from the relevant pharmacopoeia. The routine use of a secondary standard tested against the primary standard is an acceptable practice if adequately certified (USP general notices). The level of characterization of the standard is based on the intended use of the standard: examples are: - identification marker, purity, potency, … If reference standards are certified by the user relevant analytical methods should be used to assure the correct identification/ potency/purity as applicable of the standard defined. Analytical methods and techniques additional to the release specification can be used to characterize the standard. 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)
11.18	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. 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. Records of the tests carried out to identify and determine the purity should be maintained. A retest/expiration date should be assigned to the standard. It may need to be requalified. A formal certification of standards is needed when these are sent outside the control of the manufacturer.
11.19	The method of obtaining and testing secondary standards should be described in writing. 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. A retest/expiration date should be assigned. A formal certification of standards is needed when these are sent outside the control of the manufacturer.

11.2 Testing of Intermediates and APIs

11.20	Appropriate laboratory tests means 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, M7 and existing guidance on metal impurities.
11.22	The intent of this section is to pro-actively ensure trends/changes in impurity profile are identified and acted upon accordingly. The frequency of review of the purity profile versus historical batches can be based on: - campaign length - number of batches produced over a period of time - Analyses of statistical process data - Trend analyses of analytical data - Using continuous process verification This should be documented in writing and approved by the quality unit.
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	Authentic: true, accurate record of results obtained, signed (also electronically) by authorised person (from Q-Unit) and dated for every batch (API and/or Intermediate) that is released from the manufacturing site.
11.41	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). Retest and expiry dates are calculated from the manufacturing date.
11.42	Actual values should be reported if numerical results are obtained. If the result is lower than the limit of detection (LOD) the result is reported as "not detected" (ND). If the result is between the LOD and limit of Quantification (LOQ) the result is reported as < LOQ. Results above the LOQ must be reported with the actual numerical result. Non numeric results can be reported as "Conforms or complies". 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. 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.
11.43	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. The certificate of analysis should allow traceability to the original manufacturing site(source) and the way to contact the organisation that issues it.
11.44	

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. The following documents may be used as guidance: – ICH Q1A: Stability Testing Guidelines: Stability Testing of New Drug Substances and Products. – ICH Q1B: Photostability Testing of New Active Substances and medicinal Products. – ICH Q1E - 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. For intermediates, shipped outside the company control data should be available to support the required storage period and distribution conditions. For intermediates stored on site data should be available if necessary to support the defined retest period.

11.51	Follow the requirements of Section 12.8 for validation of test procedures used in stability testing. 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. Setting up a mass balance can help justifying the selection of method(s).
11.52	Ideally there is a stability sample for each pulling point stored in a miniaturised container equal to the commercial package. If technically not possible, storage of different individual bags in the same primary package for each pulling point of the API in the same small-scale secondary container is acceptable. Sample containers for multiple pulling are no longer considered as "state of the art".
11.53	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.
11.54	The batch put on stability monitoring should be representative for routine production. When stability of API is beyond two years the annual batch only needs to be tested at 0, 12, 24, 36… months. 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. Annual stability monitoring should also consider reprocessed batches – for each type of reprocessing the batch should enter the annual surveillance programme. 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	
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	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 a studies based on test results of materials. (eg. Stored under normal warehouse conditions). 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.
11.61	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. Based on the ICH Q7 Q&A document it is allowed to extend the API retest date 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. Multiple retesting to extend the API retest date of a specific batch is acceptable. The time between testing and use should be limited and justified. Material with an expiry date assigned cannot be retested to extend the shelf life.
11.62	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.
11.63	Retention samples should not be used. When performing a retest, 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..(eg. When containers from the same batch are stored at different locations/regions, outside the control of the original manufacturer).

11.7 Reserve/Retention Samples

11.70	Reserve/retention samples should be representative of the batch . It is not necessary that packaging and storage conditions of reserve samples are equivalent to those of the stability samples. The storage area for reserve/retention samples should be monitored for temperature and if applicable, also for humidity. The storage conditions should be equal or better than the label storage conditions. .
11.71	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). 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).
11.72	–

Chapter 12 Validation

12.1 Validation Policy

12.10	**Overall Policy** 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 companies rationale towards validation and detail how it will approach each key activity. The policy should reflect the expectations of the Health Authorities validation guidelines Responsibilities and roles should be clearly defined and documented to ensure that commitment is made at the appropriate level.
12.11	**Critical Parameters/Attributes** **general considerations:** A critical process parameter is a parameter in the full process (from introduction of the starting material to the final API) that has an impact on a quality attribute of the final API. To assure non-critical process steps are manufactured within the pre-defined specifications of that particular step "Key" process parameters can be defined to assure compliance to the individual specs. A critical material attribute is a specific parameter of the material which if not controlled will impact the final API quality. A risk assessment should be performed to map out critical parameter attributes prior to validation. (for example ICH Q8 and Q11) These parameters need careful consideration as they will form the basis for assessing the system to be validated. Ranges used for each critical parameter should be well defined and supported by development data and/or historical data. The parameters, if not adequately controlled, could affect the critical quality attributes of the -API. Further details on critical parameters can be found for example in ICH Q11, FDA guideline (FDA Guidance for Industry – Process Validation: General Principles and Practices) and 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	**Validation should extend to those operations deemed to be critical.** Protocols used in validation (process, analytical, equipment, facilities, IT, utilities…) should encompass those operations deemed to be critical. Once validated, any change need to follow change control procedures to evaluate the impact on the current validation status of the operation. Non-critical operations need not to form part of the validation study or not to the same extent, for example, non critical IPC's. .

12.2 Validation Documentation

12.20	**Review and Approval** Review and approval of protocols prior to the initiation of validation activities needs to come from personnel who are competent and have the authority to support the validation. Roles and responsibilities should be clearly described to assure commitment is made at appropriate departmental level.
12.21	**Acceptance Criteria** The validation protocol should refer to completion of unit operations qualification and analytical methods validation before initiation process validation. The protocol must specify all critical and key 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 criteria. Acceptance criteria are defined in validation protocols in order to assure robustness and consistency of the manufacturing process. Depending on the specific process (change) extra validation activities may be needed, examples are; homogeneity, drying profile, quality of individual centrifuge loads,…. The validation protocol should specify the batch release strategy and the need to include the batch(s) in the stability program
12.22	**Deviations Observed** All deviations related to the validation exercise should be documented and critical deviations must be fully explained in the validation report. Conclusions of the impact of the deviation on the validation exercise and corrective actions need to be documented. 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.
12.23	The validation report should reflect the explanation for the variation. The protocol does not necessarily need to be amended. Traceability should be assured

12.3 Qualification

12.30	For full comment on Qualification see ISPE Baseline Guide on "Qualification and Commissioning". • Design qualification is documented evidence that : – user requirements document has been established by production and 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 should consist in formal approval of: – meeting minutes – facility layouts – PID – Supplier detailed layout • Design qualification should apply to (in terms of equipment and/or automatic operation) : – new process – new step in actual process – modification of an equipment in a process – – IQ: 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) – PQ can be considered at the OQ part 2 or as part of the Process Validation.

12.4 Approaches to Process Validation

12.40	**Process Validation** 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. 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,…).
12.41	
12.42	– Prospective validation can be performed: - traditional way (3 consecutive successful batches) - Enhanced way based on quality by design using design of experiments and continuous quality improvement As part of the continued process verification life cycle approach
12.43	**Concurrent validation** 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 predefined acceptance criteria in the protocol, before the entire validation study is complete.
12.44	–

12.45	**Retrospective Validation** APIC advises to perform a prospective approach for such situations taken into account previous batches through statistical evaluation Retrospective validation requires a protocol that covers in detail the acceptance criteria and batch information that will form the basis for validation. Batches that fail to meet specification or are out of trend need to be discussed. 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. APIC advises not to use retain samples as they are needed for potential complaint support and critical quality defect investigations. Use of retention samples (remaining from QC testing) for this purpose is the preferred option

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
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	**Revalidation** Product Quality Reviews (PQR) (see 2.5) should assess the requirement for revalidation. Significant changes made to systems/processes or significant changes in product quality (see chapter 13) will require evaluation for revalidation. 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..

12.7 Cleaning Validation

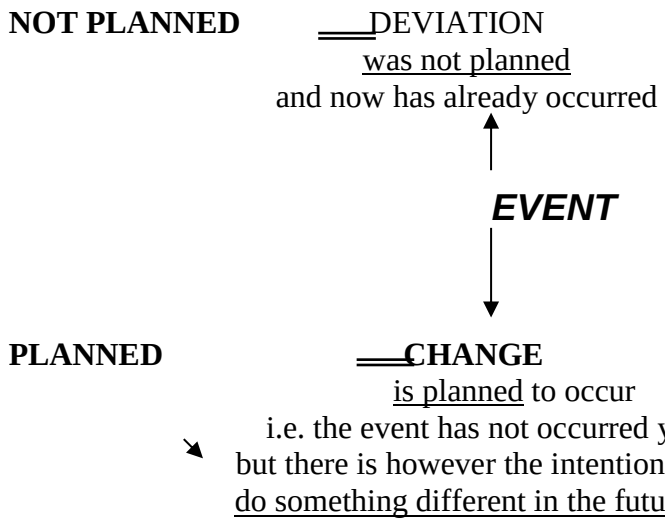
12.70 –	See APIC guide on cleaning validation for full comment: http://apic.cefic.org/pub/APIC_Cleaning_Validation_2014.pdf

12.8 Validation of Analytical Methods

12.80,	Analytical methods used directly from recognised standard references (e.g. Pharma-

12.81	copoeia) need only to be demonstrated suitable for use. System suitability tests can be found in European Pharmacopoeia. 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. The level of the validation required for in-process controls should be evaluated depending on the influence on the final API quality. Guidance on the levels of analytical method validation can be found in ICH Q2(R1). Minimum analytical validation requirements related to the type of test can be found in USP General Chapter <1225> validation of compendial procedures. APIC advices to perform analytical method validation for Starting Materials and critical raw materials, 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
12.82	**Appropriate qualification** Qualification can be performed in house or provided by the equipment supplier or qualified contactor. If supplier qualification information is used it should be approved by the Quality Unit as suitable for its intended use. If the supplier is used as a contractor and should be handled in accordance to the requirements specified in Chapter 16 Qualification of contract labs is fully described in the APIC document "guideline for qualification & management of contract quality control laboratories", http://apic.cefic.org/pub/Draft_GuidelineSupplierQualification_ContractLabsFinal_201201.pdf
12.83	Modification needs to be covered by a change control system.

Chapter 13 Change Control

13.10	–
13.11	Having defined the quality of an intermediate or API, usually in terms of a specification, 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. 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, etc. 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.  As preparation for a possible Change TRIALS are often initiated. TRIAL is defined as something that is planned for a limited time.

	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. Although in very small companies, not operating under a Quality System, "Changes" may have been agreed verbally between staff involved, 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 and approved. If there is even a slight possibility that the proposed change could cause the production or control to be different, then this proposed change 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.

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

Activity in the Change Process	**Relevant ICH Paragraph**
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 **review**ing 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 etc). The **Regulatory Affairs** unit generally would also be asked to judge whether and where the change, if internally **approve**d, 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.	§ 13.14
⇓	
Review and summarise the answers and prepare the **Approval (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

	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). Some unit should draw up a list of customers who could be effected by the proposal. The fact that the words **reviewed and approval** 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 vein 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.
13.13	The wording indicates that although **a classification procedure may help** such a classification procedure was not a requirement of a CCS. 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. 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.
13.14	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. 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. 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. This is however not the only way of ensuring that the requirements of this paragraph are met.

13.15	The intention of this Sub-section is that there should be a review of the effect of the introduced change upon the products effected, be it by a process change, be it by a change in the testing procedure, or be it due to changes in other factors which may affect the quality of the products. As this is an activity, it should be recorded hat 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).
13.16	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 always to add samples from the modified process to the stability monitoring programme. 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. 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, 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 addition 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.
13.17	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). 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 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 is an entirely new chapter in a GMP guide, 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, 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 second precaution is to quarantine the materials. This may be done by giving the material a special symbol in the Material Management computer to indicate that it is not in Quarantine awaiting test, but has already been tested and found deficient. Where such a system is not available, then simple 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" during the discussions in the WG to indicate quite clearly that, in the cases of intermediates and APIs, further processing is one option of treating materials not meeting specification. Nevertheless the input specification of the material has to be met. 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. § 2.15 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" 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. 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 definition of "Rejected" in the Guide it is left to each company to lay down its' own policy on this topic in writing. A reasonable policy would usually 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. This procedure should also cover API starting materials which are returned to the supplier as being unsuitable for use, such returns however should be accompanied by the provision that the supplier should not just blend the "returned" material with good batches and then resubmit this.

14.2 Reprocessing

14.20	The word Reprocessing was originally chosen by the CEFIC / EFPIA Working group to indicate that one was dealing with a Repeat of a PROCESS step which had already been carried out. In spite of the considerable rewording that went on after the publication of the CEFIC /EFPIA guide, this concept has been retained. Thus the essential element of REPROCESSING is that it is not a deviation from an existingly-decribed process but is solely a repeat of this. One might therefore argue that reprocessing is thus automatically covered by the original process description, (although most companies do still mention in their process descriptions from which steps "reprocessing" may be initiated. The § 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 not packed into a partially filled drum, but are returned to the process and are either blended with the next, or subsequent batches, or are even re-dissolved and re-crystallised out. If reprocess had only been permitted for defective material, such reprocessing of "tailings" (as they came from acceptable batches) would not have been permitted. 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 was not objectionable. 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. The Barr judgement on the interpretation of GMP as applied to solid dosage forms of medicinal products (e.g. tablets)

	and given in a court case in the USA in February 1993, even went so far as to state that if more that 10% of tablet batches needed to be reprocessed then the process was considered no longer validated, but the EWG did not accept this principle for intermediates or APIs due to the much greater variability in the factors which might make reprocessing necessary, e.g. APIs from materials of natural origin. The examples given are only examples of typical reprocessing steps and reprocessing is NOT limited solely to these examples.
14.21	–
14.22	The examples given in these two paragraphs were added to give additional guidance to those persons unfamiliar with the concepts of "reprocessing".

14.3 Reworking

14.30	The definition of "rework" should be fully understood before any decision to "rework" a batch is taken. This is because reworking involves another process which may not be covered by the original process description. Thus in many countries "reworked material" may not be used commercially until approval of the authorities has been obtained. The only exception to this rule would be if "alternative processes" had been approved and it was clear that material originally made by the one process could be "reworked" using the alternative and approved process. The important part of this section is the requirement that NO reworking should be initiated before the reason for the non-compliance has been determined (i.e. the "investigation" should have been completed).
14.31	–
14.32	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.

14.4 Recovery of Materials and Solvents

14.40	Recovered materials DO NOT have to meet the same specification as the original materials, and although in most case the specifications will be laxer 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. 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.
14.41	Specific approval is also given for recovering solvents, which not only makes economic sense, but is environmentally more friendly. Again 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 laxer 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.
14.42	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. Recovered solvents only being reused in the same process, i.e. being recycled, will need less testing than those being recovered and then possibly being used in totally different processes. In the former case it might be adequate to solely check refractive indices or specific gravities and maintain these within an accepted range whilst in the later 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. The criteria of "suitability" does not necessarily mean meeting the original specification, (as is discussed in § 14.41 above).
14.43	The documentation required here can, in most cases, only be of a general nature, unless the quantity of recovered solvents per batch can be measured. This is very rarely the case when solvents are continuously recovered in a campaign or in continuous production. In such cases it may only be possible to record how much new solvent is being added in what period of time to make up for losses caused by the recovery process. It is not expected that records more detailed than those required for economic purposes such as a record of the overall use of materials should be retained. However the record should indicate whether the solvent had been recovered from the same or from a different process, to help in identifying unknown impurities if these start increasing during the production campaign.

14.5 Returns

It is important to realise that this Section equally applies to Agents, Brokers, Traders, Repackers and Relabelers, as stated in § 17.80. As companies who physically treat APIs, e.g. micronizers, or granulators will automatically have to Repack" the product after such treatment this section applies to such companies also.	
14.50	When material has been returned, simply 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 taken which would later be replaced with the label indicating the decision taken, e.g. "RELEASED for REPROCESSING" or "RETURN to ORIGINAL MANUFACTURER". The second precaution is to quarantine the materials. This may be done by giving the material a special symbol in the Material Management computer to indicate that it is not in Quarantine awaiting test, but has already been tested and later returned. Where such a system is not available, then simple 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).
14.51	The difficulty is knowing under what conditions the returned material has been shipped or stored. 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 may be little doubt as to the quality in many cases these doubts will be present. This means therefore that such material SHOULD NOT be returned to the market.

	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.
14.52	The "use or disposal" of the returned material will obviously include whether it was reprocessed, reworked (or even "recovered") and which batch number the reprocessed, reworked (or even "recovered") material was given after the reprocessing, reworking (or even "recovery"). Such batches will then need new processing, packaging, labelling and distribution records as required for example by §6.5, § 6.6, § 9.4, § 10.2 etc.

Chapter 15 Complaints and Recalls

15.10
The complaint investigation has to include the impact assessment of other batches potentially involved from the same product or different product(s) (multipurpose facilities).

A period to close complaint investigations should be defined. If not possible to close the investigation timely an interim report should be prepared.

15.13 to 15.15

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).

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.

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.

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 finished dosage form manufacturers. Even notifying local and national health Authorities in case of life threatening situations can only be made in tight cooperation with the finished dosage form manufacturers, 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. There was the wish to specifically include "Contract Micronisers" in the title, but as "manufacture" includes any production step then contract micronising is thus automatically included in the application of this chapter.	
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, and when, how and where were they processed, and when were they packed, labelled and stored.
16.11	The EWG of ICH Q7 chose the word "evaluation" (rather than "audit") to indicate that it would not always be necessary to physically audit the potential contract manufacturer if there was sufficient knowledge available to ensure that the contract acceptor would be in compliance with GMP. If however the work being given out under contract included "critical process steps" and the potential contractor possibly had little experience of GMP then a site audit by a person(or persons) experienced in API GMPs would be highly recommended. It is worth pointing out that serious consideration should be given to audit laboratories inexperienced in GMP, carrying out contract testing, In such cases guidance should be given to the contract laboratory (particularly in unequivocal record keeping) to ensure that the quality standard of the activities will be in compliance with the Q7 requirements.
16.12	Although it is very rare that work carried out under contract is not covered by a written contract, (which will usually cover the extent and cost of the work to be done) the important point that is very often neglected is a clear agreement between the parties as who is to be responsible for the specific responsibilities of the Quality Unit. In particular who will carry out what analyses before and after any production work has been carried out, and who will actually release the material for further use, (including supplying to the market in the case of repackers, or contract micronizers etc.). Lines of communication between contract giver and contract acceptor should be included in the contract and this should include the names / positions of the contact partners.
16.13	As was pointed out in § 16.11 it may not always be necessary to physically audit the contract acceptor, however, as clearly stated here, the contract giver should always be allowed by the contract to audit if he so desires. This should be clearly agreed before any contract is signed, and should be a condition of signing.
16.14	Even if "sub-contracting" is not specifically mentioned in the contract under no circumstances should the contract acceptor pass on to any other company any of the work entrusted to him. Even passing on such work to another facilities located at a different site should be expressly forbidden as these could totally negate the "evaluation" which

	may have been carried out, unless this was actually approved by the contract giver.
16.15	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 (and one should not tear out pages from bound notebooks to give these to the contract giver). 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. Such records should be stored at the contract acceptor at a minimum according to the guidance given in Q7, § 6.13.
16.16	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. However it is stated again here to make it clear to those companies who have had little experience of working under GMP that "changes ARE NOT PERMITTED" unless these have been approved by the contract giver. If however the contract includes wording such as "developing a process", including "adapting the test methods where appropriate" then the contract giver has specifically requested that changes should be made, and this paragraph would not be applicable. Under such circumstances it is the responsibility of the contract giver to ensure that material produced or tested under such a contract is only used when it meets any regulatory requirements.

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

17.1 Applicability

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

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

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.

17.2 Traceability of Distributed APIs and Intermediates

17.20	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. Although the word "should" has been used in this section, nevertheless any Agent, Broker, Trader, Re-packer, etc. who is not retaining the full list of these required documents would need to have comparable documentation which fulfils exactly the same purpose. 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. It is essential that the identity (i.e. name) and the address **of the <u>original</u> manufacturer** be given to the customer (see also § 17.61. If the Agent, Broker, Trader, Repacker, etc. does not know or cannot provide the name and address of the original manufacturer of the commercially available intermediate or API this would then be a serious violation of this GMP Guide. 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. It should be pointed out that in the EU, if a "Qualified Person" releases a Medicinal Product made from an API from an unknown manufacturer this would be a serious violation of his/her ethical duties as a "Qualified Person". The inclusion of the wording "authentic" Certificates of Analysis is to indicate that it is <u>not acceptable</u> to photocopy the Certificate of Analysis of the original manufacturer onto the letter heading of the Agent, Broker, Trader, etc. 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 In General the customer should receive all necessary information to fulfill his Regulatory and Legal obligations.

17.3 Quality Management

17.30	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

17.4 Repackaging, Relabeling and Holding of APIs and Intermediates

17.40	See 7.11 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

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	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. 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 of course cover any changes made by the manufacturer to the process, the specifications (specifically the deletion of a test parameter) the test methods or the retest date.
17.61	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 a current expectation that traceability must be assured over the full supply chain and a system should be in place to control supply chain integrity.
17.62	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.
17.63	If a request is made to an Agent, Broker, Trader, Re-packer, etc. for a Certificate of Analysis all the requirements listed in § 11.4 (Certificates of Analysis) must be met. 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 in a NEW Certificate of Analysis showing the name and address of the laboratory that carried out the NEW tests. It would not be acceptable to replace the original val-

	ues 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. 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). 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.

17.7 Handling of complaints and recalls

17.70	It is a current expectation that any complaint or request for recall should immediately be informed to the related customers and suppliers.
17.71	It is a current expectation that the investigation outcome and corrective/preventive actions defined should be informed promptly to the customer(s). And it is also current expectation that a system should be in place to assure a recall of all products involved can be accomplished in a timely manner. A regular Mock recall audit/exercise, on the **most complex** distribution system, is advised to be performed and documented. Legal time frames for reporting potential recalls to Health Authorities and customers should be followed.
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.

17.7 Handling of returns

17.80	It is a current 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 or storage conditions are not available or known rejecting and destroying the product is advised.

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 dependant 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 antibacterials 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 down stream 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	–

Chapter 19 APIs for Use in Clinical Trials

19.1 General

This subject has been covered extensively in the APIC document **"GMP for API Development"** (http://apic.cefic.org/framecommunica.html). Some practical hints are included below.	
19.10 – 19.11	There are many differences between the production of commercial APIs in a chemical plant and the production of chemical supply in a research /development facility. The research/development environment is characterised by limited information about process, analytical methods and data; also by work on a small scale and a high level of expertise of individuals involved. Making changes for process and product improvement is part of it's activities.

19.2 Quality

19.20 – 19.25	A Quality Unit for the Development function should be in place, and also an SOP covering the quality system to be applied. Even if testing is performed outside the R&D function (other function in the company or an outside contractor) the responsibility for data gathered and recorded should remain inside the R&D function, assigned to the QU. All analytical results obtained should be recorded, checked and traceable. To allow traceability, a defined 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, like milestone reviews. A labelling system, in accordance with the identification system in place, should be applied to each substance/sample.

19.3 Equipment and Facilities

19.30 – 19.31	All equipment used in laboratory scale preparation should be appropriate to the task, in good working order, and clean. Lab equipment qualification (e.g. glassware) can't be expected. Qualification of pilot scale equipment should be considered. To minimise product contamination or cross contamination, appropriate measures should be taken into account. Some common lab operations, like vacuum filtering or drying in an oven where other products are also dried, are potentially sources of contamination or cross-contamination. Preventive measures should be in place when performing such operations, like covering with filter paper or other appropriate films.

19.4 Control of Raw Materials

19.40 – 19.41	A systematic approach for raw materials reception, testing and acceptance / release decision should be in place. Beware that on-the-shelf reagents can be contaminated.

19.5 Production

19.50	Any deviation from normal operations should be documented. Process documentation

– 1951	should contain references to raw materials, chemical reaction / isolation pathway, process equipment, process parameters, any unexpected finding and obtained yields. When existing, process deviation investigations are recorded.

19.6 Validation

19.60 – 19.61	No validation is required because wording allows interpretation that validation is needed when more than "a single batch" is produced, and Development activities are by nature changing processes. The chemist may have an idea of which parameters are critical, but will not have performed the reaction enough times to establish the acceptable ranges. The information gathered during the development phase will become the foundation for the validation of the commercial process. Guidance on Cleaning Validation is given in the "GMP for R&D" document (reference see beginning of chapter 19).

19.7 Changes

19.70	Changes are part, as described above, of the development phase. Changes should be recorded for late information, but not subject to a formal change control system. The significance of the possible changes should be evaluated by scientists in other disciplines (toxicology, formulation, etc.), who use the API in the (new) drug development process.

19.8 Laboratory Controls

19.80 – 19.82	At early stages, product characteristics are often unknown. Testing methods based on sound scientific principles can be applied, and refined as knowledge is gained on products and their relevant properties. This information will become the foundation for setting the raw materials, API starting materials, the intermediates and API specifications. Sample retention should be defined and followed according to a plan. Samples are considered as part of the batch/experiment documentation. Expiry and retest dates are not relevant during development steps, but materials should be tested for its suitability prior to use. Data collected can afterwards justify process time limits (see 8.2).

19.9 Documentation

19.90 – 19.92	All process and testing relevant information should be available. A system for record keeping and archive should be in place. Data may be required to support registration. In addition to the records, process and analytical methods history should be also documented to justify the setting of ranges for critical points, and remain available for late evaluation. The basic information of process development should be selected, at the end of the research and development phase, and kept as long as the product is available commercially. Failed reactions records are useful information for the investigation of full scale batch failures.

Chapter 20 Glossary

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