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Principle	This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products. It is a GMP requirement that manufacturer's control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 should also be taken into account.	Computerized systems is just one type of equipment that has to be qualified. It should not be addressed in the "principle". If there are particular aspects to be addressed for computerized systems it should be done in an own chapter as it is done for test methods. Missing statement, if this Annex is applicable to API manufacture also. There seems to be a conflict between the qualification/validation requirements as they exist in Part II and the new Annex 15 (which applies to Part I and Part II). In consequence, a modification of Part II seems to become necessary.
General	A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of validation and qualification should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. The principles in ICH Q8, Q9, Q10 and Q11 or other systems guaranteeing at least the same level of product quality and security should be used to support validation and qualification activities. Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own validation programme may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.	No "other systems" should be allowed since this would mean that tthis annex will notj be the standard to comply with.
1.	**ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION**	
1.2	Validation activities should only be performed by suitably trained personnel who follow approved validation procedures.	This is also valid for qualification activities. Therefore "qualification" should be added.
1.3	Validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function, however there should be appropriate oversight over the whole validation life cycle.	This section is unclear. The expectations are not defined.
1.5	The VMP should be a summary document which is brief, concise, clear and contain data on at least the following: c) Summary of the facilities, systems, equipment, processes on site and the current validation status. d) Template formats to be used for protocols and reports. g) Handling of acceptance criteria	It is difficult to have a document which is always up to date. A review time frame should be defined c) qualification and validation d) A same template for all the divers equipments has no added value. What with external protocol? g) Acceptance criteria have to defined. What is the meaning of handling ? Changing? Is it the process of defining acceptance criteria?

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	j) The ongoing validation strategy, including revalidation and / requalification, where applicable. k) Confirmation that the materials used for validation are of the required quality and suppliers are qualified to the appropriate level.	j) This section is unclear. In which way does the assessment need to be challenged? (Number of people, training needed….). Ongoing validation strategy is unclear. It's in contradiction with the terminology of ongoing process verification (ex continued process verification) and/or k) It is quite difficult to confirm via the VMP that the selected suppliers are adequate.
1.6	For large and complex projects, planning takes on added importance and it may be necessary to create a separate VMP.	This phrasing could be deleted.
2.1	Good documentation practices are important to support knowledge management throughout the validation lifecycle.	The term "validation lifecycle" is not correct here. The knowledge management must be assured throughout the lifecycle of the product. Therefore it is essential to have a good documentation practice within validation activities.
2.3	The relationship between documents in complex validation projects should be clearly defined and any inter-relationships documented.	New vocabulary relationship instead of cross-reference.
2.4	A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important and the acceptance criteria for each.	This paragraph should be reworded to make it clearer.
2.9	A formal release for the next step in the validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.	The next step in the validation should be defined (URS, FAT, SAT, DS, IQ etc…) (see 3.11) Failing to meet the acceptance criteria during validation should not be overruled.
new	To be added	When a validation activity is performed by a Third Party it should be done in close cooperation with the manufacturer. Reports should be thoroughly reviewed and approved by adequate personnel of the responsible manufacturer.
3.	**QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES AND UTILITIES**	
3.1	Validation and qualification activities should consider all stages from initial development of the user requirements specification or initial process development through to the end of use of the equipment, facility or process. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:	The paragraph should be rewritten completely focussing on qualification of equipment, facilities and utilities. At the moment it is mixing qualification, validation and different stages of the life cycle (process development) and therefore becomes very unclear. The word "validation" should be deleted. This section covers the qualification activities only (see headline). Criteria have to be considered and defined.
3.2	The specification for new facilities, systems or equipment should be defined in a URS and/or a functional specification.	URS and FS are two different documents each with their own purpose. They cannot substitute each other.

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	The essential elements of quality need to be built in at this stage and any GMP risks minimised. The URS should be a point of reference throughout the validation life cycle.	What is meant by GMP risks? Better: “Risk Assessment considerations should be reflected in the URS in order to minimize risks related to product quality.”
3.3	The next element in the validation of new facilities, systems or equipment is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should also be verified during the design qualification.	“Validation” should be replaced by “qualification”. We are talking here about design qualification (DQ) of equipment. What are the requirements for a proper DQ?
3.4	Equipment, especially if incorporating novel or complex technology, should be evaluated at the vendor prior to delivery.	The expectation of evaluating FAT is too strong. Add “if applicable, …” FATs are engineering and constructions activities.
3.6	Where appropriate and justified, documentation review and some tests could be performed at the FAT stage without the need to repeat on site if it can be shown that the functionality is not affected by the transport and installation.	FATs are engineering and constructions activities. If the company wishes to use FAT or SAT test results this should only be done in a secure way (no exchange in between FAT and delivery).
3.7	FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.	FATs are engineering and constructions activities. Most of the time the installations aren’t commissioned.
3.8	IQ should be performed on new or modified facilities, systems and equipment.	A statement is missing, what should be done during IQ (should be here, not in the glossary).
3.9	IQ could include, but is not be limited to the following:	“should” instead of “could”
3.10	OQ normally follows IQ but depending on the complexity of the equipment it may be performed as a combined Installation/Operation Qualification (IOQ). OQ could include but is not be limited to the following:	A statement is missing, what should be done during OQ (should be here, not in the glossary) “should” instead of “could”
3.11	The completion of a successful OQ should allow the finalisation of maintenance plans, standard operating and cleaning procedures, operator training and preventative maintenance requirements.	The formal release is no longer mentioned as it was in the previous version. There is no longer an obligation to finalize this step (see 2.9)
3.12	PQ should follow the successful completion of IQ and OQ.	A statement is missing, what should be done during IQ (should be here, not in the glossary) Some contradiction to point 3.13 It might not be necessary for simple and pieces of equipment.
3.14	PQ could include, but is not be limited to the following: b) Tests should cover the operating range of the intended process, unless documented evidence from the development phases which confirm the operational ranges are available.	“should” instead of “could” They are no longer any ranges described . Worst batch sizes is not clear. Which evidence can confirm the operational range?

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4.	**PROCESS VALIDATION**	
4.1	The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and ongoing process verification.	It might be better to replace “ongoing process verification” by “re-validation”. Re-validation is one aspect of the ongoing process verification. As the chapter deals with process validation aspects only, the focus should be laid on re-validation in this paragraph.
4.3	Medicinal products may be developed using a traditional approach or a continuous verification approach however irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes should undergo a prospective validation programme wherever possible prior to marketing of the product.	A hybrid approach is also possible (see 4.24) and should be mentioned here already. The last sentence could be moved to the beginning of the chapter.
4.4	Process validation for new products should cover all intended marketed strengths and sites of manufacture, however for products which are transferred from one site to another or within the same site, and where there is existing product knowledge, including the content of the previous validation, the number of validation batches could be reduced by the use of a bracketing approach. This approach could be acceptable for different strengths, batch sizes and pack sizes/ container types if justified.	“may” instead of “could” Bracketing approach is always a difficult challenge. It should be specified how such a bracketing should be designed (key elements to cover). It should be stated where it would not be accepted (eg aseptic filling, sterilization, milling, ..?)
4.5	For the site transfer of legacy products, the manufacturing process and controls should comply with the Marketing Authorisation and meet current expected licensing standards for that product type. If necessary, variations to the Marketing Authorisation should be submitted.	Should this to be in the annex 15?. This belongs in Part I. “must” instead of “should”
4. 7	Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified. e.g. for a continuous manufacturing process.	Some contradiction with § 4.4
4.8	Facilities, systems, utilities and equipment used for process validation should be qualified and test methods should be validated.	Add: and used measuring devices should be calibrated.
4.14	In exceptional circumstances where there is a strong risk – benefit to the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP and approved by authorised personnel.	Very theoretical, especially for many companies when small product volumes are manufactured. Concurrent validation for products with low risk should be allowed.
4.17	The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.	Using the traditional approach the number of batches used for the validation should not be less then 3. A minimum of 3 batches should be kept explicitly.
4.18	Without prejudice to 4.17, it is generally considered acceptable that a minimum of	A minimum of tree consecutives batches should remain. Companies will always justify

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	three consecutive batches would constitute a validation of the process although an alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.	that one batch will be enough .
4.20	Validation protocols should include, but are not be limited to the following: f) monitoring/recording equipment) together with the calibration status. h) Proposed in-process controls with acceptance criteria and the reason(s) which each in-process control is selected.	Missing points: - Bracketing / Matrixing approach (if applicable) - Number of validation batches (if applicable) - External partners (e.g. Labs, micronizers) - Document references f) Add: "..and qualification" h) ??
	Continuous process verification	The term "verification" as designation for the new validation approach is confusing, particularly as it is followed by the step of on going process verification. It should be clearer differentiated between the validation step and the verification step within the product life cycle. Therefore "continuous process validation" seems to be the much better and clearer nomenclature.
4.22	The process verification system should be defined and there should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.	This section encloses different general quality items. The wording used is unclear and the paragraph should be restructured. It is unclear what is mentioned by "process verification system". Is it a new validation approach (continuous process verification) or the ongoing process verification?
4.24	A hybrid approach using the traditional approach and continuous process verification for different production steps can also be used. Where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data, continuous verification may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.	Should be mentioned in an own chapter or section as it is done for the other two approaches, not as a subchapter of the continuous process verification.
	Ongoing Process Verification during Lifecycle	A statement is missing, what should be done (purpose, content)
4.25	Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends	It is not clear whether the ongoing process verification is only applicable when the continuous process verification approach is chosen or whether it is applicable in any

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	evaluated.	case, regardless which approach has been chosen (traditional, new or hybrid). It is not clear what activities are expected here, which have not been already covered by today's requirements as PQR, Change Control and re-validation. If it is the intention to describe a new approach of monitoring the robustness of a manufacturing process throughout the life cycle of a product, this step should be clearly distinguished from the continuous process verification step and it therefore should be addressed in an own chapter. More details should be given for: a. How to proceed with toll manufacturers producing only few charges of a product? b. Is it necessary to establish a separate "OgPV master plan" or could it be integrated in the MVP? c. Does the Marketing Authorization Holder (MAH) have to review / read / approve the OgPV Reports? Is there a role for the MAH? d. How to proceed with toll manufacturers producing only few charges of a product? e. Scope of the OgPV (whole process?)
4.26	The extent and frequency of ongoing process verification should be reviewed periodically and modified if appropriate, considering the level of process understanding and process performance at any point in time in the product lifecycle.	A minimum frequency suggestion for the documentation and acceptance of verifications will be helpful for industry and regulators. More guidance should be given regarding the responsibilities to review/approval of OgPV outcome (similar to the PQR chapter).
4.28	On going process verification should be used to support the validated status of the product in the Product Quality Review, however, incremental changes over time should also be considered and the need for any additional actions (e.g. enhanced sampling) should be assessed.	The connection to PQR should be clearly described (and ongoing stability?). Isn't there a need to adapt the chapter 1.4 related to PQR requirement accordingly to streamline with the new OgPV requirements? This is a discrepancy with the glossary definition. Indeed the definition takes in account only the process. It is redundant with section § 4.30.
4.29	On going process verification should be considered where any individual change or successive incremental changes during the product lifecycle could have an impact on the validated status of the process.	The connection to change management should be clearly described. How can we have evidence that a company has enough knowledge to evaluate the impact of a change?
5	**VERIFICATION OF TRANSPORTATION**	
5.1	Finished medicinal products, investigational medicinal products, bulk product and samples should be transported in accordance with the conditions defined in the Marketing Authorisation, product specification file or by the manufacturer.	Scope missing (transport to pharmacies / patients?) In which form should this be specified and on what basis?

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6.	**VALIDATION OF PACKAGING**	
6.1	Variation in equipment processing parameters during primary packaging may have a significant impact of the integrity and correct functioning of the pack (e.g. blister strips, sachets and sterile components) therefore primary packaging processes should undergo validation.	What should be done for secondary packaging? “to” instead of “of”
6.2	Qualification of the machine settings for the types of pack above should be carried out at the minimum and maximum operating ranges defined for the critical components parameters such as temperature, machine speed and sealing pressure or for any other factors.	The terminology used is inadequate. The paragraph refers to validation.
7.	**VALIDATION OF UTILITIES**	The title should be Qualification of utilities and the chapter (7) should be moved into the Qualification section (3).
7.1	The quality of steam, water, air, other inert gases, coolants etc. should be confirmed following installation using the qualification steps described in section 3.	Only “gases” (not “inert” gases)
9.	**CLEANING VALIDATION**	
9.2	A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation however, it is not acceptable for this criterion alone to be used. Repeated cleaning “until clean” is also not considered an acceptable approach.	Is (instead of “may form” Delete “important part” Why? If the company can show that it is sufficient? (e.g. herbal extracts, Zinc oxide) Delete “also”
9.3	It is recognised that a cleaning validation programme may take some time to complete and validation with ongoing verification after each batch may be required. The level of data from the verification to support a conclusion that the equipment is clean should be evaluated.	The wording ‘’ongoing verification’’ brings confusion with the terminology ‘’ongoing process verification’’. The appropriate chronology and equivalence between the traditional and the enhanced validation approach are not respected. For non English natives it would be preferable to use the right definition. If a process (separately or overall) is not approved nor considered valid then only the terminology ‘’continuous process (cleaning, etc…..) verification’’ should used.
9.5	Limits for the carry over of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value. (See EMA guidelines on setting health exposure limits). The justification for the selected PDE value should be documented in a risk assessment which includes all the supporting references. The removal of any cleaning agents used should also be confirmed. Acceptance criteria should consider the potential cumulative effect of multiple equipment in the process equipment train.	IMPs should be addressed in this section as well. As in § 9.12.

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9.7	Where campaign manufacture is carried out, the impact on the ease of cleaning between batches should be considered and the maximum length of a campaign (in both time and number of batches) should be the basis for cleaning validation exercises.	Where campaign manufacture is carried out, the cleaning between batches should be considered and the maximum length of a campaign.
9.8	Where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed. When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility. Worst case cleaning validation should be performed for each cleaning method used.	Delete and each worst case product (if more than one).
9.9.	Cleaning validation protocols should detail the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.	Also sampling method and test method
9.10	Sampling should be carried out by swabbing or rinsing at the last stage of cleaning or by other means depending on the sampling location. The swab material should not influence the result. If rinse methods are used, the sampling should be performed during the final rinse in the cleaning procedure. Recovery should be shown to be possible from all materials used in the equipment with all the sampling methods used.	Or after the final rinse?
9.11	Typically the cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.	The § 41 from the current GMPs PE 009-11 (Annexes) 1 March 2014 v. "Test until clean" is not considered an appropriate alternative to “cleaning validation”. The missing paragraph should be reinstated. 3 times should be specified as a minimum
10.	**RE-QUALIFICATION**	Chapter 10 could be shifted to either chapter 3 or ongoing process verification
10.3	Where manual processes are used, such as for cleaning of equipment, the continued effectiveness of the process should be confirmed at a justified frequency.	The term ‘’continued’’ in this section is confusing and should not be used in conjunction with the term ‘’Re-qualification “as it is to close to the ongoing process verification. For each person? With regard to the terminology used, re-qualification (see title of chapter) of the cleaning process is not consistent and rather be a re-validation. Thus, the effectiveness of cleaning processes should follow the principles of the ongoing process verification strategy. Integration of paragraph 10.3 into chapter 9 should be considered.
	GLOSSARY	
	Bracketing approach: A validation scheme/protocol designed such that only batches on the extremes of certain predetermined and justified design factors, e.g., strength, batch size, pack	Bracketing approach, is a delicate subject. Companies use it extensively and it isn’t guaranteed that it will work. It should be stated that the first batch of a non validated batch type will be produced, the batch must be tested in accordance with all validated attributes and parameters.

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	size are tested during process validation. This approach assumes that validation of any intermediate levels is represented by the extremes validated. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.	
	Continuous process verification An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)	Definition is unclear. The key elements of the new approach that separates it from the traditional approach must be mentioned here. The continuous process verification is still a process validation. Even in this document it is integrated in chapter 4, which is called “Process Validation”. It is therefore not an alternative to process validation but a different, a new way to do it. In awareness that this is the official ICHQ8 definition, it should at least here be tried to give a better picture of what is really meant.
	Ongoing Process Verification (also known as continued process verification) Documented evidence that the process remains in a state of control during commercial manufacture.	The definition of “Re-Validation” from the current GMPs PE 009-11 (Annexes) 1 March 2014 v. is missing and should remain as the traditional approach. *’’A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality’’.*
	Process Validation The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.	Re-validation see Ongoing process verification
	Re-Validation A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.	Not present in the version of February 6, 2014.See comments Ongoing process verification
	State of control A condition in which the set of controls consistently provides assurance of continued process performance and product quality.	The term ‘’continued’’ in this section is confusing. See comment § 10.3.
	Traditional approach A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.	The definition proposal covers the enhanced approach as well. A clearer proposition should be suggested.