ENGINEERING PHARMACEUTICAL INNOVATION

Proposed Regulation/Guidance Document: **EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation**

Comments submitted by: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT (if any)
The term, "justified" appears numerous times in the document. Is there a standard of justification? If not "justified, approved, and authorised by appropriate personnel" is suggested as implied in 2.2. This would be similar to the wording in 4.14.
Cleaning process terms are not harmonised throughout the document, e.g., cleaning methods, cleaning process, cleaning procedures. The use of "cleaning process" only is recommended.
The use of the terminology 'Qualification and Validation' is not consistent throughout. For example Section 1.1 states 'All qualification and validation'….etc. For the remainder of section 1, the Qualification term is not used. This could be clarified in a note to ensure there is no ambiguity.
Section 3.4 – 3.7 (FAT/SAT). Current best industry practices for equipment qualification is to utilize the data obtained from FAT and SAT to support qualification activities, with the appropriate controls in place to do so *e.g.* change control. Due to utility constraints at vendor sites, it is typically the SAT functional testing that offers the greatest opportunity to support the qualification effort. This section, particularly the statement in 3.7 'FAT may be supplemented by the execution of a SAT….etc.' understates the significance of the SAT in current industry best practices. Other specific comments also apply to this section.
9.12 For investigational medicinal products or products which are only manufactured infrequently**, cleaning verification** may be used instead of cleaning validation. . The term cleaning verification vs validation is not made clear nor defined in the glossary. Given there is an item in the Glossary on **process verification** some general introduction clarifying the use of verification terminology would be useful.
Related other draft guidelines, such as " Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, EMA/CHMP/ CVMP/ SWP/169430/2012" and "the Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1)" are not referred. Some items, such as "carry over limit based on PDE" and "hybrid approach", seem to suddenly appear and their rationale is not clear in Annex 15 alone.

GENERAL COMMENTS ON THE DOCUMENT (if any)
The chapter of “Process Validation” overlaps considerably with the Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). Since the Guideline on process validation is more detail , it is suggested to more simply describe the chapter and refer to the Guideline.
The ‘ongoing process verification’ in the draft talks about monitoring product quality by use of statistical and other tools. However the guideline does not explicitly mention monitoring of critical material attributes and other process variables like critical process parameters which will reflect on the adequacy of process controls to deliver quality product consistently.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ formatting and text proposed for addition with **bold and underlining**.

Section Number	Current Text	Proposed Change	Rationale and Comment
General	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.	As part of a quality risk management system, decisions on the scope **and extent of qualification and validation** 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 qualification and validation** activities. Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own **qualification / 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.	To be consistent, qualification is prior to validation. Data obtained from outside sources can be used for supporting both qualification and validation activities
Principle	The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 should also be taken into account.	The relevant concepts and guidance presented in ICH Q8, **Q9**, Q10 and Q11 should also be taken into account.	Q9 is integral to Q8 Q10 and Q11
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.	This Annex describes the principles of qualification and validation which are applicable to the facilities, **systems**, equipment, utilities and processes used for the manufacture of medicinal products.	"3.2 User Requirement Specification", "10. Re-Qualification" and other sections include a reference to "systems".
Principles	Computerized systems used for the manufacture of medicinal products should be validated according to the requirements of Annex 11.	Computerized systems used for the manufacture of medicinal products should **also** be validated according to the requirements of Annex 11.	Annex 15 applies to an automated equipment from an equipment qualification and a process validation point of view nevertheless Annex 11 applies to the automated equipment as well because it is a computerised system
1.1	All qualification and validation activities should be planned and take the life cycle of equipment, process and product into consideration.	All qualification and validation activities should be planned and take the life cycle of process and product into consideration.	The life cycle of "equipment" is not defined in related ICH guidelines and some gaps of interpretation will occur. Also Principle dose not describe the life cycle of equipment.

Section Number	Current Text	Proposed Change	Rationale and Comment
1.2	Validation activities should only be performed by suitably trained personnel who follow approved validation procedures.	**Qualification and validation activities should only be performed by suitable trained and qualified personnel following approved procedures and/or protocols.**	Qualified personnel should perform qualification and validation. Personnel qualifications include training and experience. Procedures to be followed could include corporate procedures, operating procedures, etc.
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.	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 **Quality** oversight over the whole validation life cycle	Leaving this to "appropriate" oversight leaves this important quality system aspect potentially outside the "oversight" of the quality unit. This is not thought to be the purpose or intent of Q8/Q9/Q10/Q11 ."Quality" oversight will ensure issues raised to executive management.
1.5	The VMP should be a summary document which is brief, concise, clear and contain data on at least the following:	The VMP should be **brief, concise, clear and minimally address / describe the following:** **d)Format and content of protocols and reports** **e) DELETE THIS LINE** **i) DELETE THIS LINE** **k) DELETE THIS LINE**	The idea that VMP is a summary misses the point. The VMP is the foundation not the summary. And setting the VMP out to be "brief" seems to contradict the long list of "things" that need to be included within it (11 different things, each of which probably have multiple other documents supporting them).
1.5 b)	The organisational structure for validation activities.	The organisational structure i**ncluding roles and responsibilities (e.g., RACI chart) for validation activities.**	It must be clear, in a commissioning or qualification activity, what the accountability and responsibility is for each participant in order to ensure decisions and approvals have traceability to the appropriate authority.
2.2	All documents generated during validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.	All documents generated **for qualification and validation activities** should be approved and authorised by a representative of the Quality Assurance function.	Logical addition
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.	**Validation protocols should be prepared for quality impacting systems. Protocols should define the critical aspects, critical quality attributes and critical process parameters which may impact product quality or process control and the acceptance criteria for each.**	More detailed and specific explanation consistent with current ICH terminology

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2.40	A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important and the acceptance criteria for each.	A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important and the acceptance criteria for each. **Alternately, a formally issued procedure may be used in lieu of a protocol.**	For situations where the same procedures and acceptance criteria may be used for multiple pieces of equipment, the qualification may occur per procedure using controlled forms for documenting results as opposed to the use of a unique protocol and report.
2.8	The conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.	The conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria **either as part of the validation report approval or as a separate summary document**. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.	Added text allows for the summary to be included as part of the validation report without the need for an additional summary document. This text reflects the same wording as section 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."
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 there is a documented assessment that there is no significant impact on the next activity	**Formal release for routine operation on completion of the project phase in the qualification or validation process should be authorised by the relevant responsible personnel. Conditional release can be given where compliance with acceptance criteria or deviations have not been fully resolved if there is a documented assessment of the impact and appropriate controls in place.**	It is possible to have a post approval part in for example a PQ that allows you to release certain parts of the system with the need for a report or a separate summary document
3.2	User requirements specification (URS) The specification for new facilities, systems or equipment should be defined in a URS and/or a functional specification. 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.	User requirements specification (URSs) The specification **critical aspects** for new facilities, systems or equipment should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks minimised. The URSs should be a point of reference throughout the validation life cycle.	Focus requirements on critical aspects and to align with the first paragraph of the document "Principle" - "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. URs are where critical aspects should be defined and URs should not be confused with general engineering detailed design specifications.

Section Number	Current Text	Proposed Change	Rationale and Comment
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.	**Design Qualification is the first formal Qualification activity.** **Within DQ:** **• Requirements specifications are finalised.** **• Compliance of the design with requirement specifications is assessed.** **• Compliance with GMP is assessed and risk control processes prescribed.** **• Critical components are identified.**	In general, systems and equipment are qualified and processes are validated. Also reworded to say that facility, equipment and system design should be verified against user requirements during design qualification.
3.4	Equipment, especially if incorporating novel or complex technology, should be evaluated at the vendor prior to delivery.	Delete Section 3.4	FAT is an engineering step. FAT should not be performed depending on the equipment novelty or complexity, but based upon a risk assessment. FAT and SAT should be implemented in accordance with the agreement between Supplier and Manufacturer. This regulatory requirement for FAT and SAT appears inappropriate - see also comment in 3.5 below
3.5	Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site unless otherwise justified.	Delete Section 3.5	Exactly where acceptance testing is performed is a business decision. The requirement should be for the equipment to meet with GMP and URS only. See also comments 3.4 3.6 and 3.7
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.	**Verification (document review and testing) can be performed at any stage in the equipment implementation lifecycle as long as final functionality / installation is not impacted / changed by transport and installation.**	Consistent with comments in section 3.4 & 3.5
3.7	FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.	Delete Section 3.7	Consistent with comments in section 3.4, 3.5 and 3.6
3.9	IQ could include, but is not be limited to the following: (a) Installation of equipment, pipe work, services and instrumentation as detailed in the design and confirmation of current engineering regarding drawings and specifications. (b) Verification of the correct installation against pre-defined criteria.	IQ **should** include, but is not be limited to the following: **Verification of the correct installation of critical equipment, pipe work, services and instrumentation as detailed in the design and confirmation of current engineering regarding drawings and specifications against pre-defined criteria.**	IQ is verification of installation, not the installation activity. Limit IQ to verification of critical aspects of the installation by combining and re-wording lines a) and b). See also comment in section 3.14 regarding the use of the word “could”.
3.10	b) Tests to confirm upper and lower operating limits, and /or “worst case” conditions.	**Tests to verify the critical operational functions of the systems and equipment.**	Alternative wording to clarify that OQ verifies critical functionality.

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3.14	PQ could include, but is not be limited to the following:	PQ **should** include, but is not be limited to the following:	Using the word "**could"** seems to imply that there are no things that "should" happen and that instead PQ is completely optional. The word "could" has also been used in other sections eg 3.9 and a similar comment applies.
4.10	For process validation batches, production, development, or other site transfer personnel may be involved.	**Process validation batches should be manufactured under conditions that represent routine commercial production.**	This sentence is not clear and is difficult to understand. A suggested alternative is provided however if this is not the meaning then an alternative/additional sentence may be required.
4.10	It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding when commercial manufacture starts.	Delete Sentence	Statement implies that validation batches and commercial batches are mutually exclusive. A validation batch can be a commercial batch.
4.14	*Concurrent Validation (written in italic)*	**Concurrent Validation**	The reason for this title to be in italics is not clear..
4.14	….there is a strong risk-benefit to the patient…….	….t**here is a strong benefit versus risk to the patient….**	The intent here appears to be to show that the benefit is strong, versus the risk, which justifies concurrent validation.
4.20	"It should also be noted that a lifecycle approach is applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production."	"It should also be noted that a lifecycle approach is applied linking product and process development, **and** validation of the commercial manufacturing process **whilst the** process is maintained in a state of control during routine commercial production."	The wording in the last sentence of 4.2 is structurally unclear and hard to understand. The intent appears to be to imply that using the life cycle approach gives a more robust state of control - however this is not actually clear. A suggested modification is given but this is not ideal. It may be better to encapsulate the meaning in a number of shorter sentences.
4.20	"Validation protocols should include, but are not be limited to the following:"	"Validation protocols should include, but are not limited to the following:"	**"Be"** doesn't belong; or else it could read, "…but are not to be limited…"
4.20 f)	e) List of the equipment/facilities to be used (including measuring/ ~~f)~~ monitoring/recording equipment) together with the calibration status.	e) List of the equipment / facilities to be used (including measuring / monitoring /recording equipment) together with the calibration status.	Error in document. 4.20 f) is a continuation of e), and the lettering thereafter needs adjusting

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4.27	On going process verification should be conducted under an approved protocol and a corresponding report should be prepared to document the results obtained.	Ongoing process verification should be conducted under an approved protocol **or procedure. Data should be statistically analysed and results obtained should be continually monitored to assess the state of control.**	On occasions having a separate protocol may not be holistic enough. For situations where the same procedures and acceptance criteria may be used for multiple pieces of equipment, the verification may occur per procedure using controlled forms for documenting results as opposed to the use of an unique protocol and report.
5.2	It is recognised that validation of transportation may be challenging due to the variable factors involved however transportation routes should be clearly defined.For transport across continents seasonal variations should also be considered.	**Transportation routes should be evaluated for seasonal variation and validated unless suitable continuous monitoring is performed and reviewed prior to release of product at local depots.**	The influence of seasonal variations may exist within continents and even large or multi climate countries. Also transportation routes may not be pre-determined or qualified provided suitable continuous product monitoring is performed and reviewed prior to release of product at local depots.
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.	The **quality of product / process contact utilitiy fluids and gasses** should be confirmed following installation using the qualification steps described in section 3.	The addition of “coolants” will lead to confusion re requirement for qualification as they are not direct product contact.
7.2	The period and extent of qualification should also reflect any seasonal variations, if applicable, and the intended use of the utility.	The period and extent of qualification should also reflect any seasonal variations, if applicable, and the intended use of the utility. **Continuous verification of critical process parameters can also be used to demonstrate compliance during seasonal variations.**	Continuous verification could be applied to demonstrate that seasonal variation is taken into account.
7.3	A risk assessment should be carried out where there may be direct contact with the product e.g. HVAC systems or indirect contact such as through heat exchangers to mitigate any risks of failure.	**A risk assessment should be carried out where there may be direct contact with the product/process stream via fluid / air transfer with indirect contact utilities.**	Rewording in line with comment 7.1
9.1	Recovery should be shown to be possible from all materials used in the equipment with all the sampling methods used.	Recovery should be shown to be possible from all materials used in the equipment with all the sampling methods used. **Risk assessments can be used to determine which materials require recovery studies.**	It has been documented in literature that the various stainless steel materials tend to have the same recovery and that recovery factors for materials that are only a small percentage of the equipment train do not impact the overall results.

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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.	A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation however**, its reliability and effectiveness should be verified using an appropriate alternative method unless supported through science based risk assessments.**	The visual check for cleanliness should be acceptable if its reliability has been confirmed by swab sampling and a validated analytical method, such as HPLC determination.
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.	**There should be sufficient** data from the verification to support a conclusion that the equipment is clean.	Clarification of sentence meaning. If 2nd sentence remains unchanged, please reconsider whether the sentence is needed at all. The term "verification" mentioned in the first sentence says the same.
9.4	Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities should be validated. Where a manual process is used, an assessment should be performed to determine the variable factors which influence cleaning effectiveness, e.g. operators, the level of detail in procedures such as rinsing times etc. For manual cleaning, if variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.	Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities should be validated. Where a manual process is used, **a risk** assessment should be performed to determine the variable factors which influence cleaning effectiveness **and performance** e.g. operators, the level of detail in procedures such as rinsing times etc. ~~For manual cleaning, if variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.~~	For manual cleaning processes the primary concern is performance (i.e. batch to batch repeatability) and not effectiveness alone. The risk assessment will identify the conditions for the cleaning process.
9.5	Limits for the carryover of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value.	Add **Refer "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, EMA/CHMP/ CVMP/ SWP/169430/2012"**	"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, EMA/CHMP/ CVMP/ SWP/169430/2012" should be referred.
9.5	Acceptance criteria should consider the potential cumulative effect of multiple equipment in the process equipment train.	Acceptance criteria should consider the potential cumulative effect of multiple **items of** equipment in the process equipment train.	There may be a language or terminology difference.
9.6	The potential for microbial and, or if relevant, endotoxin contamination, should be assessed during validation. The influence of the storage time before cleaning and the time between cleaning and use taken in to account to define (dirty and clean) hold times for the cleaning validation.	The potential for microbial and,~~or if relevant~~ endotoxin contamination, should be assessed ~~during~~ **prior to** validation. The influence of the storage time **after use and** before cleaning and the time between cleaning and use **should be taken in to account when defining** (dirty and clean) hold times for the cleaning validation.	Greater clarification and the use of a risk assessment for the identification of hazards

Section Number	Current Text	Proposed Change	Rationale and Comment
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 impact on the ease of cleaning between batches should be considered and the maximum length of a campaign (in **terms of time'** number and size of batches) should be the basis for cleaning validation exercises.	Batch size variability may be normal, but the impact on cleaning could be significant.
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.	the impact **of the campaign length on the ease of cleaning after the completion of the campaign** should be considered	We find it difficult to understand that there could be an impact of the campaign length on the ease of cleaning **between each batch.** The campaign length may, however, have an impact of the ease of cleaning after the **last** batch.
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.	Where a worst case product approach is used as a cleaning validation model, **a scientific rationale should be provided for the selection** of the worst case product ~~should be justified~~ **The impact of new products on the selection of the worst case should be 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.~~	Clarification of impact of new products and use of worst case. The first sentence indicates worst case is one option. Worst case cleaning parameters are challenged during cleaning method development, not during validation.
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.	Cleaning validation protocols should detail the locations to be sampled, the rationale **based on a risk assessment for the selection of these locations** and define the acceptance criteria.	Gives a sound basis for selection rationale
9.10	Sampling should be carried out by swabbing and/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.	**Depending on the sampling location, sampling should be performed by swabbing, by rinsing, or by other means at the last stage of cleaning.** **The sampling materials should not influence the result.** **Recovery studies from materials used in the equipment should be based on risk assessment for each sampling method used.**	Clarification.. (3rd sentence…) This is applicable only when the rinse sampling solution is same as the solution used for final rinse. A separate rinse is needed (after the cleaning of the equipment) if the sampling solution is different. Recovery studies for **all** materials may not be necessary. A risk-based approach to all activities should be undertaken.

Section Number	Current Text	Proposed Change	Rationale and Comment
9.10	Where different equipment is grouped together a justification of the specific equipment selected for cleaning validation is expected.	Where different **products** and equipment are grouped together **a scientific** justification of the specific product and equipment selected for cleaning validation is expected.	The grouping strategies include products and equipment, they should be scientifically justified.
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.	~~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.	Clarification.
9.13	Where cleaning validation has shown to be ineffective or is not appropriate for some equipment, dedicated equipment should be used for each product.	Where cleaning ~~validation~~ has shown to be ineffective or is not appropriate for some equipment, dedicated equipment should be used for each product.	It is not the validation, which is not effective; it is the cleaning. "You can validate a poor process; it still is a poor process."
9.13	Where cleaning validation has shown to be ineffective or is not appropriate for some equipment, dedicated equipment should be used for each product.	Where cleaning validation has shown to be ineffective or is not appropriate **(e.g. carry-over limits are too low for analysis),** dedicated equipment should be used for each product.	To explain why cleaning validation might not be effective.
10.1	"… an appropriate frequency to confirm …"	"… an appropriate frequency **based on the risk assessment** to confirm …"	The risk assessment should give input to the review frequency
10.2	Furthermore the possibility of incremental changes should be assessed.	Furthermore the **possible impact** of incremental changes between qualifications should be assessed.	Clarification
11.60	Supporting data should be generated to confirm that the impact of the change has been demonstrated prior to approval.	Supporting data should be generated **(where possible)** to confirm that the impact of the change has been **determined** prior to approval.	There are cases where supporting data can't be generated until the change is made, so if the change can't be made without approval, the data can't be generated. "Demonstrated" doesn't make sense in this context.
Glossary	Cleaning validation is documented evidence that an approved cleaning procedure will remove all traces of the previous product used in the equipment.	Cleaning validation is documented evidence that an approved cleaning procedure will remove all traces of the **active product or other relevant ingredients in the** previous product used in the equipment **, and cleaning agents if used, and bioburden to a level that do not represent a risk to the patient using the product manufactured thereafter.**	It is not necessary and practical, and many times even not possible to remove all traces of the previous product. It is also not necessary and practical to provide documented evidence to demonstrate removal of all the components of the previous product,, besides the active ingredient. For the remaining ingredients a risk based approach can be applied, to include for example organic solvents if they are part of product or cleaning agent formulation. On the other hand cleaning agents and bioburden aspects should be considered.

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Glossary	Knowledge management	Add reference (I**CH Q10**)	Like (ICH Q8) in Design Space
Glossary	Worst Case A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.		The parameters used should be based on an assessment of the product and process and should provide the worst case challenge.
Glossary	None	Add: User Requirements Specification (URS) – The set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.	This is a critical document in the lifecycle of any production system. For mostly custom systems or facilities, a URS should be created with enough specifics to enable competing designs that satisfy requirements.
Glossary-Cleaning Validation	Cleaning Validation definition: remove all traces of previous product	Use other published definition..	Removal of **all** traces is not possible Also, cleaning validation is not just about removal of previous product.