EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Final, 27th May 2014

Submission of comments on '**Revision of EC Guidelines on GMP Annex 15: Qualification and Validation'**

Comments from:

Name of organisation or individual
EFPIA

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EFPIA welcomes the revision of Annex 15 to the EU GMP Guide to reflect the current and state-of-the-art guidance impacting process validation, as well as the use of Quality Risk Management and reference to latest ICH guidance. We also feel the Annex could further benefit from addressing the following: **Evolving technologies** Some of the detail is too prescriptive (see detailed comments – page 7 onwards) to allow other established accepted methods, new methods or emerging technology to be fully utilised. The Annex should be written with a consideration of future trends and technologies. For example, there is likely to be an increasing need in the future to concurrently 'validate' products earlier in the lifecycle as a result of the potential for adaptive licensing, and release of phase-2 development product to small patient populations. In addition, the level of detail in the document may prevent other established accepted methods or new methods to be fully utilised. For example, in section 9.10, where direct surface measurement techniques may be used in the future, rather than current swabbing and rinsing techniques. **Terminology** • We welcome the inclusion of life-cycle concepts of process validation which brings some level of harmonisation with other available guidance. However, the consistency within this draft needs some improvement, for example in clarity of terminology, and improved alignment with the recently published EU Process Validation guidance document. • EFPIA also believes that use of the term 'Traditional Approach' is inappropriate in a GMP Guideline, since the principle aims of validation remain unchanged and it is	

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	anticipated that at some point in the future what are currently considered 'new' approaches could be considered to be 'traditional'. Suggestions for alternate text are proposed in the detailed comments. • Better consistency with respect to the usage of the terms 'validation', 'verification' and 'qualification' can avoid misunderstanding and misinterpretations. It appears the terms may be used interchangeably in some cases. It is recognised that the terms 'validation' and 'verification', particularly when used in relation to processes, have evolved from the original understanding that verification was a one-time event that demonstrates compliance with an acceptance criterion, whilst validation was a demonstration that a process is capable of routinely achieving compliance with criteria. • EFPIA proposes that glossary text should provide definition, but omit unnecessary 'guideline language'. See for example the comment to 'bracketing approach'. **International alignment** Whilst respecting regional guidelines, there should be alignment as far as possible with other existing key international process validation guidelines, which are binding for industry. EFPIA recognises the efforts in this regard but believes there may be additional opportunities for further alignment to avoid both divergence as complexity driver and misinterpretation by both industry and regulators. In particular it is apparent that there is still confusion in industry about the differences between 'continuous process verification' from ICH Q8 and 'continued or on-going process verification', especially where translation of these concepts from English must be considered. In this respect the use of the term 'on-going' is easier to translate than 'continued'. However, the 'continuous process verification' concept could remain unclear. EFPIA suggests that further dialogue, possibly exploring practical experience and/or the development of Q&As with illustrative examples could be helpful (see, for example, detailed comments on 4.25)	

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	Process verification review frequency The concept paper for the Annex 15 revision stated that: "no adverse impact on industry in terms of resources or costs is foreseen." Hence, with regard to the on-going process verification, it should be clarified that the frequency of review may not be higher than once a year as for the Product Quality Review. This means that data from on-going process verification can be used to support the Product Quality Review, and should be reviewed and reported periodically, at least annually. **Cross references to other guidelines** There are parts of the Annex that cover technical contents of other EU GMP Chapters, ICH Guidelines, Note for Guidance on Validation, or the calculation of health-based cleaning limits. We recommend that cross references should suffice, for example: • Section 5: Qualification of Transportation, as it is described in the EU Good Distribution Practices, • Sections 9.5 and 9.8: the methodology to deduct cleaning validation acceptance limits should not be subject to Annex 15. It is noted that health-based limits are still under discussion (EU GMPs chapter 3, 5, and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'). The additional detail in section 9 may unnecessarily limit the approaches that may be employed to meet the expectations, especially as the Guideline on health-based limits has not yet been finalised. • Section 11: the expansion of section 11 Change Control seems to extend the scope of the document beyond validation. For example, Change management is a key element of any Quality system, therefore should be addressed in general chapters of Eudralex Volume 4 rather than this section.	

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	Principle section The 'principle' section of the document should clearly indicate the scope of the decision-making with respect to Quality and GMP with relation to Process Validation. For example, the justification to perform concurrent validation on the basis of patient risk-benefit' is clearly not solely a quality decision but requires medical input (see 4.14). **Section 3** This section should tie Installation, Operational and Performance Qualification (IQ, OQ and PQ) back to quality risk management, as one of the goals of this revision is to connect to ICH guidance on quality risk management. We propose to add a general statement prior to paragraph 3.1 that refers to a quality risk based approach for any and all of the subparts of section 3. Also, it should be clarified that Factory acceptance testing (FAT) and Site acceptance testing (SAT) are not always part of the qualification process but could be recommended preliminary or complementary steps that could be leveraged as part of the overall qualification. Hence organisation and rules applicable to qualification need to be interpreted flexibly when applied to FAT/SAT (e.g. vendor's roles and responsibilities, documentation, deviation management). **Discussion in a workshop** Finally, EFPIA believes a workshop on the guidance prior to the publication of the final text would be helpful in addressing the above points.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Table of Contents		**Comment**: the Table of Contents lists section 7 as 'Qualification of Utilities' but the actual heading is 'Validation of Utilities'; it may also be more logical to include this section within section 3 'Qualification Stages for Equipment, Facilities and Utilities'. **Proposed change**: to consider re-ordering the chapters as explained above.	
1.3		**Comment**: the wording in this section could be improved/ strengthened. **Proposed change**: reword the sentence as follows: "There should be quality oversight throughout the entire validation life cycle, however validation personnel do not have to report into the Quality function."	
1.4, 1.5 and 1.6		**Comment:** Validation planning is a critical step in the overall lifecycle. There would be benefit in reflecting in sections 1.4 and 1.5 that there is a 'high level' or 'site' validation plan to define the overall approach and governance for the validation process. Section 1.6 could then be used to illustrate that validation plans may additionally be used to cover specific projects. **Proposed change:** 1.4 The key elements of the site validation programme should be clearly defined and documented in a **Site** validation master plan (VMP) or equivalent document. 1.5 The **Site** VMP should be a summary document which is brief, concise, clear… 1.6 For ~~large and complex~~ projects, **validation** planning takes on	

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		added importance and it may be necessary **or more appropriate** to create a separate VMP."	
1.5		**Comment:** the text reads that the summary document should 'contain data', though most of the listed items do not have associated data. We are not sure of the value of adding content requirements to the VMP, such as template formats (d), resource assessment (i)… Those contradict the briefness of the VMP. Instead, cross-reference to existing SOPs describing those should be enough. Overall, the annex should focus on what rather than "how to" details. **Proposed change:** Section 1.5: The VMP should be a summary document which is brief, concise, clear and ~~contain data~~ **describe** ~~on~~ at least the following': a) Validation policy **and strategy** b) The organisational structure for ~~validation activities~~ **management of validation activities, for example, responsibilities and reporting lines for validation personnel** d): delete – could be referenced to general procedures; too specific for a master plan g): it is not explained what "handling of acceptance criteria" means. If this is intended to mean how acceptance criteria will be determined, that intent should be made clear. i): Delete – already covered under general GMP. j) ~~The ongoing validation strategy, including revalidation and / requalification, where applicable~~. **The strategy to maintain the validated state, including revalidation, requalification where applicable.** k): delete – already covered under GMP	

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2.1		**Comment:** 'Good documentation practices' is not defined as such **Proposed change:**"An appropriate documentation practice (see EU-GMP, Chapter 4) is important …	
2.2		**Comment**: the paragraph should be reworded. **Proposed change:** revise the text to read: "All documents generated during **each step of qualification and** validation should be approved and authorised by appropriate personnel."	
2.4		**Comment**: this paragraph should be reworded. **Proposed change:** revise text to read: "A written validation protocol should be prepared which defines the critical systems, ~~attributes, and parameters which are important,~~ and the acceptance criteria for ~~each~~ **the attributes and parameters which are important**."	
2.5		**Comment:** this statement needs to be further defined, as it can be interpreted in different ways: 1) 'third party' is a documentation expert hired by the manufacturer to author/create validation protocols for the manufacturer's use, or 2) 'third party' is a contract manufacturing site where they author/create validation protocols, however they must comply with their internal procedures, cGMPs and Quality Agreements in place between the parties. The contract giver may require certain validation requirements from the 'third party' within the Quality Agreement. **Proposed change:** "Where ~~validation protocols are supplied by~~ a third party **is providing validation services**, the manufacturer should confirm suitability and compliance with company procedures before approval **of validation documents.**"	

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2.6		**Comment**: the requirement to process any changes to the approved protocol within the deviation system is preventing other equally valid and compliant ways to report, address and analyse such as minor changes that can be written into the protocol itself (e.g. typographical errors/equipment reference number). **Proposed change:** "Any changes to the approved protocol during execution should be documented ~~as a deviation and be scientifically~~ **and** justified".	
2.7		**Comment**: deviations from the pre-defined acceptance criteria should be documented in the qualification-/validation report. **Proposed change:** revise text to: "Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation, be investigated and any implications for the validation **status** discussed in the report."	
2.8		**Comment**: the conclusion of the validation should include comments and analysis. **Proposed change:** rephrase to read: "The conclusions of the validation, **including any comments and analysis**, should be reported and the results obtained summarised against the acceptance criteria."	
3.1		**Comment:** there is no mention of Commissioning and Qualification or the Verification approach as currently practiced in the industry. This draft of Annex 15 does not acknowledge the progression from conventional equipment qualification to the more contemporary processes defined by both e.g. ISPE and ASTM and widely accepted in the industry. The text should be extended to clarify that analytical equipment is included.	

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		Proposed change: ‘<u>Qualification activities apply to new and modified equipment (including analytical equipment), facilities and utilities. A risk-based and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety should be used. Qualification 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. Typical 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</u>.’	
3.4, 3.5 and 3.7		**Comment**: flexibility needs to be incorporated into the guideline regarding the requirements and use of FAT and SAT in the qualification process (e.g. compare simple laboratory equipment with a filling machine). Clarification may be needed that FAT and SAT are not, strictly speaking, part of the qualification process but are recommended preliminary or complementary steps. Organization and rules applicable to qualification and listed in sections 1 and 2 may not apply to FAT/SAT, for example vendor's roles and responsibilities, documentation, deviation management will usually differ. The current structure of section 3 may lead to various interpretations. **Proposed change:** add after 3.7 “**<u>FAT and SAT support the qualification process but are not always part of it. As such, FAT and SAT follow specific management rules and criteria, which may differ from those defined in sections 1 and 2 for qualification</u>**.”	

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3.11		**Comment:** it is not clear what the difference is between "maintenance plans" and "preventive maintenance requirements" **Proposed change:** use the wording of current Annex 15, sect. 15, i.e.: "The completion of a successful Operational Qualification should allow ~~finalisation of maintenance plans, standard operating and cleaning procedures, operator training and preventative maintenance requirements~~ **the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements**."	
3.14		**Comment:** a): a risk-based (bracketing) approach to PQ testing should be allowed for systems that handle large combinations of components, such as secondary packaging equipment. This could alternatively be discussed in section 4. **Proposed change:** revise the text to "a) Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions ~~with worst case batch sizes~~ **and across the intended batch size range**. The ~~frequency of~~ sampling **strategy** used to confirm process control should be justified." "b) Tests should cover the **intended** operating range of the ~~intended~~ process~~, unless d~~. Documented evidence from the development phases which confirm the operational ranges ~~are available~~ **may be used**." Add a new bullet c): '**A bracketing approach may be used to optimize the testing plan**.'	
4.3		**Comment**: see general comment about the use of 'Traditional approach' – term is not needed here to explain the principle.	

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		Proposed change: '**Irrespective of the approach used to develop a medicinal product, 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**.'	
4.4		**Comment**: we believe it should be possible to use previous product knowledge and process validation data to also allow bracketing for **new** products. The Guideline on Process Validation already indicates that in section 4: "Process validation can be performed in a traditional way…, however there is also the possibility to implement continuous process verification if an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience". **Proposed change: add: 'For new products, bracketing should be permitted, if there is enough knowledge available and a justification is provided**.'	
4.14		**Comment:** the assessment of patient risk-benefit can not be done by validation personnel, but is typically subject to a management decision making process. Clear criteria should be given as to when concurrent validation is acceptable. **Proposed change:** to amend as follows: "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."	

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4.16		**Comment**: see general comment about the use of 'Traditional approach'. Although used in the CHMP Guidance, the term is not needed here to explain the principle, and is inappropriate in a GMP Annex. **Proposed change**: new heading: **'Process validation by confirming reproducibility'** and amend 4.16 to: "**A frequently used approach for process validation is where a number of batches of finished product are manufactured under routine conditions to confirm reproducibility**."	
4.17, 4.18		**Comment**: it remains unclear from #4.17 and #4.18 as to what constitutes an acceptable rationale to go for 3 validation batches. A lifecycle approach to validation incorporates the concept of supplementing validation activities intended for commercialization of the product with additional data gathered from the manufacturing stage (i.e. ongoing process verification) and therefore the final sentence is not required. **Proposed change**: to revise 4.18 to: "Without prejudice to 4.17~~, it is generally considered acceptable that~~ a minimum of three consecutive batches **manufactured under routine conditions can be justified to** ~~would~~ constitute a validation of the process, ~~although an alternative number...used at the site. An initial validation … verification exercise.~~ **It is also acceptable to use fewer than three validation batches, when knowledge from similar products or processes is available from development or commercial scale**."	
4.20		**Comment**: the rationale for the key decision on the number of validation batches should be evident.	

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		Proposed change: add a bullet point: **"Justification/rationale for the number of validation batches**"	
4.20 (e and f)		**Comment**: bullet point f) is in fact a continuation of bullet point e) **Proposed change**: merge the two bullets points	
4.21		**Comment:** it would be possible to implement PAT-based or RTRT controls without having conducted a 'QbD approach to development'. It is not necessary to consider what is a 'QbD approach to development'. Section 4.21 should focus on the role of control strategy within the concept of continuous process verification. The use of the phrase 'routine process control' makes the elements sound very traditional and could lead to misinterpretation of the desired outcome. **Proposed change: '**~~For products developed by a quality by design approach, where it has been scientifically established that routine process control provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation~~ **Where it has been scientifically established during development that the control strategy provides a high degree of assurance of product quality, then continuous process verification can be used**.	
4.22		**Comment:** 'Process verification system' should not be introduced, as it is a novel term and misleading. The last sentence should be deleted. **Proposed change:** "The method by which process will be verified should be defined and there should be a science and risk based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. Process Analytical Technology and multivariate	

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		statistical process control tools may be used in the control strategy and to support continuous process verification."	
4.23		**Comment**: it is implied that the general principles described earlier in section 4 would apply to continuous process verification. **Proposed change:** delete 4.23 or clarify what does not apply, if anything.	
4.24		**Comment**: see general comment about the use of 'Traditional approach'. Although used in the CHMP Guidance, the term is not needed here to explain the principle, and is inappropriate in a GMP Annex. **Proposed change**: 'A hybrid approach using ~~the traditional approach and~~ **different approaches to process validation for different production steps** ~~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 on-going process verification even though the product was initially validated ~~using a traditional approach~~ **by demonstrating reproducibility of batch manufacture**.'	
4.25 to 4.29		**Comment**: the introduction of a stage that verifies the continued capability of the validated control strategy is welcomed. From the perspective of globally operating companies it would be desired that consistency of key terminology is maintained for the purpose of harmonisation. We recognise that 'On-going Process Verification' ("Documented evidence that the process remains in a state of control during commercial manufacture") is easier to translate, and the	

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		definition used is essentially identical to the established US-FDA definition for 'Continued Process Verification' ("Assuring that during routine production the process remains in a state of control"), corresponding to stage 3 in the FDA guidance. Therefore, it should be made very clear that 'on-going process verification' is the same definition as 'continued process verification' in the glossary, and that either term would be accepted by EU authorities in company documents.	
4.26		**Comment:** in the concept paper it is stated that: "No adverse impact on industry in terms of resources or costs is foreseen." Thus it should be acceptable, that the on-going process verification is not reviewed at a higher frequency than once the year like the Product Quality Review. Data from on-going process verification can be used to support the Product Quality Review, and should be reviewed and reported periodically, at least annually. **Proposed change:** the extent and frequency of ongoing process verification should be reviewed periodically, **at least annually**.	
4.27		**Comment**: a defined protocol is likely to be used for the first step of on-going verification (i.e. the production of number of batches that gives increased confidence in the ability of the now validated control strategy to produce material of the appropriate specification). This period of work should be pre-defined and reported to justify entry into routine commercial production and a reduction in sampling/testing levels to routine frequency. However it is not practicable to have a validation protocol open throughout the life of the product. There may be other ways of achieving the purpose, such as using a plan or SOP that permits change in criteria as process data is accumulated and process capability is demonstrated over time. The need for quality oversight has already been noted (paragraph 1.3)	

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		and does not need repeating here. **Proposed change:** "On-going process verification should be conducted ~~under an approved protocol~~ **using a protocol, plan or procedure** and a corresponding report should be prepared **periodically** to document the results obtained…"	
4.28		**Comment**: the current wording does not imply the applicability throughout the product lifecycle. 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. **Proposed change:** "~~On-going~~ **continued** process verification should be used **throughout the products lifecycle** to support the validated status of the product, as documented 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."	
4.29		**Comment**: requirement to address incremental changes is already addressed proactively in 4.28. Section 11 addresses change control, sentence redundant and confusing. **Proposed change**: to delete 4.29	
5. and 5.2		**Comment:** The term 'qualification of transportation' should be used instead of 'verification' or 'validation'. **Proposed change:** 5. Verification and Transportation: change to: 5. "**Qualification of Transportation**" and 5.2. 'It is recognised that ~~validation~~ **qualification** of transportation...'	

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5.3		**Comment**: studies to select primary packaging materials, performed during product development, and shipping studies performed for registration, consider the risks from conditions to which product is likely to be exposed during distribution and marketing over the shelf life of the product. These include humidity, vibration, and handling. These variables should not need to be re-assessed during a product's lifecycle except where required to support changes in packaging materials or shelf life. The routine evaluation of complaints and damages should be used to detect issues that may require changes to product specification (including primary packaging). However, transport delays, failure of loggers etc are transport process failures that do require consideration in a risk assessment. The text should cover the risk-prone elements of the transportation process and not the factors which are covered by the inherent specification of the product and its primary packaging **Proposed change** (if any): rephrase 5.3 as indicated in bold: A risk assessment should be performed to consider the impact of **variables in the transportation process, other than those conditions which are continuously controlled or monitored, e.g.** delays during transportation, failure of data-loggers, etc..	
5.4		**Comment**: the need to monitor should be risk-based. For example, it could be justified that continuous monitoring of temperature adds no value for a product with no special storage conditions, or labelled store below 25/30°C which is delayed at a temperate zone air/seaport or road hub. Registration and on-going stability studies 'cover' temperature and humidity for the climate zone where product is registered (according to ICH Q1 and QWP guidances). Likewise, continuous monitoring may not be justified for a qualified/validated passive container capable of maintaining required temperature	

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		beyond the duration of a delay. **Proposed change**: to amend 5.4: 'Due to the variable conditions expected during transport e.g. delays at airports, **a risk assessment should be performed, considering product susceptibility and environmental conditions of the route, to determine the need for** continuous monitoring of any critical environmental conditions to which the product may be subjected ~~should be performed~~.'	
6.1		**Comment**: the scope needs clarifying. **Proposed change:** to revise text to: "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 **of finished medicinal products and bulk products** should undergo validation."	
6.2		**Comment:** the introduction of new terminology should be avoided ('critical component parameters'). **Proposed change:** Retain 'critical process parameter.	
7.0		**Comment:** we consider that the term "validation" complies more with process and the term "qualification" with "utilities" **Proposed change:** Replace "validation of utilities" with "**qualification of utilities**". As a consequence, this section should be moved after the Section 3 "qualification stages for equipment, facilities and utilities	
7.1		**Comment**: the current sentence is too general and does not take into account the principle of a risk-based approach driving the qualification/validation effort. Following risk assessment, utilities (such as plant steam, compressed air for instrumentation), may only	

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		require FAT/SAT but no formal qualification (IQ/OQ/PQ). Also "coolants" should be omitted as an example. **Proposed change:** amend sentence: "**When justified by direct product impact or contact or through product risk assessment**, the quality of steam, water, air, other inert gases, ~~coolants~~ etc. should be confirmed following installation using the qualification steps described in section 3."	
7.3		**Comment:** improve the clarity of wording of this paragraph. **Proposed change:** revise the text to: "**Where utilities may have direct contact with product (e.g. HVAC systems) or indirect contact (e.g. heat exchangers), potential risks of failure and mitigation measures shall be identified through a risk assessment**."	
8.1		**Comment:** remove redundant text **Proposed change:** revise the text to: "All analytical test methods used in qualification, validation or cleaning exercises should be **qualified or** validated ~~with an appropriate…."~~	
8.2		**Comment:** microbial results are relative and not an absolute value. The method should be demonstrated to have the appropriate recovery according to EP 2.6.1, 2.6.12 and 2.6.13. **Proposed change:** "Where microbial testing of product is carried out, the method should be ~~validated to confirm~~ **demonstrated to be suitable and having the appropriate recovery in order to demonstrate** that the test product does not influence the result."	
8.3		**Comment:** it is not only on the clean rooms, can be also be for equipment that is disinfected. In addition, it is relative and not an absolute result; the method should be demonstrated to have the	

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		appropriate recovery. **Proposed change:** "Where microbial testing of surfaces ~~in clean room is carried out, validation should be performed on the test method~~ **is required as part of cleaning verification/ validation exercises, the methods should be demonstrated to be suitable and having the appropriate recovery** to confirm that the sanitizing agents do not influence the results."	
9.2		**Comment**: visual check alone should be acceptable for minor equipment (equipment that is portable and that can be 100% inspected) for example scoops, lids, etc., if supported by appropriate data and documented justification. Also the wording could be strengthened for this section. Repeated cleaning 'until clean' is inherent to the development of the cleaning process. **Proposed change:** "…for this criterion **to be used alone for major equipment (e.g. that for which surfaces cannot be 100% visually inspected). With appropriate data and documented justification, visual inspection is acceptable for minor equipment that can be 100% inspected**. Repeated cleaning "until clean" is also not considered an acceptable approach **for cleaning validation**".	
9.3		**Comment**: "…and validation with on-going verification after each batch may be required." For a process where several batches are run consecutively in a manufacturing campaign, it may be justified that cleaning is done at the end of the campaign (prior to product changeover) rather than after each batch of the on-going campaign. Cleaning after each batch within a production campaign of the same material may be unnecessary and costly.	

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		Proposed change: "…and validation with on-going verification may be required after each batch **or prior to product changeover".**	
9.5 and 9.8		**Comment**: this section is too restrictive as it only indicates the use of PDE and goes beyond that being proposed in chapters 3 and 5. In addition it indicates that residues of cleaning agents should be removed, but does not mention limits. **Proposed change**: 9.5: 'Limits for the carry over of product residues should be based on an ~~toxicological~~ evaluation ~~to determine the product specific permitted daily exposure value (PDE)~~ **that uses the principles outlined in the EU GMP chapters 3 and 5**. The justification for the selected ~~PDE value~~ **limits** should be documented in a risk assessment which includes all the supporting references. The removal of any cleaning agents to this limit should also be confirmed.' 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~~ the results of the evaluation according to 9.5 as well as solubility. Worst case cleaning validation should be performed for each cleaning method used.	
9.7		**Comment:** process residues vary and the impact of product on campaign length with respect to time and carry-over between batches is process specific. Both time and number of batches may not apply. **Proposed change:** revise text to state …"maximum length of a	

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		campaign (in ~~both~~ time and**/or** number of batches) should be the basis …	
9.9		**Comment**: cleaning validation protocols should address the sampling methodology (e.g. swab or rinse). Consequently, 9.10 should be deleted as its carries too much unnecessary detail. **Proposed change:** 'Cleaning validation protocols should detail the locations to be sampled, the rationale for the selection of these locations **and sampling methodology** and define the acceptance criteria.'	
9.10		**Comment**: The sampling methodology (e.g. swab or rinse) should be covered through 9.9. and 9.10 should be deleted. **Proposed change**: to delete paragraph 9.10	
9.13		**Comment**: change the test of 9.13 to provide proper reference to existing guidance in EU GMP chapter 3 and 5. **Proposed change:** revise text to: "Where cleaning validation has been not successful, alternative approaches have to be used to avoid carry-over as described in EU GMP chapter 3 and 5."	
10.1		**Comment**: the term 'State of control' should be avoided as it is (per Glossary definition) applicable to process performance and product quality. Contents in section 10. does not refer to processes or products. **Proposed change**: revise text to: "Facilities, utilities, systems, equipment should be evaluated at an appropriate frequency to confirm that they ~~remain in a state of control~~ **are qualified**."	
10.2		**Comment**: the section should refer to cumulative effects of incremental changes that could affect the validation state	

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		Proposed change: '… Furthermore the ~~possibility~~ **possible cumulative effect of** incremental changes should be assessed **for potential impact on the validated state**.	
11.1		**Comment**: please see General comments – an extensive discussion of Change Control is not considered appropriate in a Process Validation document as Change Control is covered elsewhere in the GMP guides. The current wording in Annex 15 may be sufficient. **Proposed change:** keep wording of current Annex 15.	
11.6		**Comment**: the wording of section 11.6 is not clear and does not add anything that is not already covered in other sections (11.2 to 11.5, 11.7) concerning change control. **Proposed change**: consider linking these sections to on-going Process Verification, as the monitoring and trending of that lifecycle stage will help confirm that changes have been successful, or have had no impact on the control strategy.	
Glossary: general comment		**Comment**: the guidance would benefit from consistency in the usage of the terms the terms 'validation', 'verification' and 'qualification' to avoid misunderstanding and misinterpretations. It appears the terms may be used interchangeably in some cases. It is recognised that the terms 'validation' and 'verification', particularly when used in relation to processes, have evolved from the original understanding that verification was a one-off event that demonstrates compliance with an acceptance criterion, whilst validation was a demonstration that a process is capable of routinely achieving compliance with criteria. **Proposed change:** to carefully review the usages of the terms verification, validation and qualification in each section. Consideration could also be given to adding definitions for Verification, Validation, and Qualification to differentiate between the concepts.	

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Glossary: specific terms			
Bracketing approach		**Comment:** although this is the same text as in the CHMP guideline, the text should be shortened to provide definition, but avoid unnecessary 'guideline language'. Where such additional 'guideline language' appears to be necessary, this should be incorporated into the Annex main text. **Proposed change:** to revise text to: "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 size are tested during process validation. This approach assumes that validation of any intermediate levels is represented by the extremes validated."	
Cleaning Validation, and Cleaning Verification		**Comment:** the definition of cleaning validation states to remove all traces of the previous product used in the equipment. This is limited by the technology to test for trace levels e.g. How would you prove that you have removed all traces? This should also include cleaning agents and not just product. Cleaning Verification is mentioned in 9.12 but not defined. **Proposed change:** "Cleaning validation is documented evidence that an approved cleaning procedure will consistently remove ~~all traces of the previous product used in the equipment~~ **residues to a safe and acceptable level, providing equipment which is suitable for further processing of medicinal products**." Consider adding a term for **cleaning verification** e.g.: "Cleaning verification is a single test, which consists of sampling, analysis and evaluation of the results, to confirm that the cleaning process has cleaned equipment to a level acceptable for pharmaceutical	

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		processing."	
Concurrent validation		**Comment**: please remove "justified on the basis of significant patient benefit" consistent with the comment on 4.14. **Proposed change:** revise text to: "Validation where, the validation protocol is executed concurrently with commercialisation of the validation batches."	
On-going Process Verification		**Comment**: the difference between continuous process verification and on-going process verification is not sufficiently clear, and several companies have raised concerns about this. We note that the definition proposed in the draft Annex 15 is consistent with the definition in the recent CHMP guidance on Process Validation but believe that it would be helpful to include the definition for 'Continued process verification' from the FDA guidance to confirm alignment. **Proposed change**: suggest including, or cross referencing, the definition for 'Continued process verification' from the FDA Process Validation guidance, i.e. 'Assuring that during routine production the process remains in a state of control.'	
Traditional Approach		**Comment**: Although the term is used in the CHMP guideline, we believe use of the term 'Traditional Approach' is inappropriate in a GMP Guideline, since the principle aims of validation remain unchanged and it is anticipated that at some point in the future what are currently considered 'new' approaches could be considered to be 'traditional'. **Proposed change:** delete the definition and adjust the text in the Annex accordingly.	

Please add more rows if needed.