<19th May 2014>

Submission of comments on "Volume 4 EU Guidelines for GMP for Medicinal Products for Human and Veterinary Use – Annex 15: Qualification and Validation"

Comments from:

Name of organisation or individual
IFAH-Europe

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
	IFAH-Europe welcomes the opportunity to comment on the revision of Annex 15 which from our point of view was necessary in the light of the changes and development which occurred since last revision in 2001. IFAH-Europe welcomes this extensive revision to align with Chapter 1, Annex 11, and ICH Q8 – 11. The new annex is a positive adaptation to the current knowledge and technology. There is more flexibility in designing the qualification, validation and technology transfer plans and acceptance criteria, based on previous knowledge, experience, and risk assessments. However, for veterinary products there is a high complexity and high number of dosage forms and species and impact on food chain (if any) and it is very difficult to assess PDE and the cumulative effect of train equipment. Also for veterinary vaccines and other large molecules, the toxicity level is very low (proteins). In addition, a lot of cleaning validation was already performed according to the old approach and it is too complex to repeat cleaning validation studies. Proposal is to keep the old approach for veterinary products and previously accepted limits may continue to apply including the specific exclusions in annex 4.	

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	Limits setting for Cleaning validation as described in this draft (page 12 §9.5) seems to only allow toxicological/PDE based criteria. This should not be the only single case as: - Outcome of workshop on dedicated facilities held in EMA London on September 30th 2013 regarding SWP's 'toxicological tool' is to provide a revised version and consider new consultation. Unless this achieved, toxicological approach cannot be finalised in new draft GMP guidance documents. - Posology/dose based limits are extensively used in Health Industry (> 50 % of cleaning validation rationales in use within companies). So far cross contamination management on this basis has never been a concern from the Authorities point of view. In many cases, calculations demonstrate that limits can be based on these criteria without leading to risk increase. Posology is information always available to establish a rationale (unlike toxicological data: species, route of administration, acute vs chronic…). - In the other regulated areas (Asia/Pacific, Africa, Latin America, and North America) thresholds and/or establishment of limits based on FDA, PIC's or other guidance is still applicable. Unnecessary constraints of re-validation will lead to substantial workload and cost in each GMP site in a competitive environment. - PDE approach is based on long term exposure that is not necessarily appropriate in such context which is by essence unique cross-contamination at product change-over. - Animal Health is to some extent very specific and cannot rely solely on human based toxicological/PDE criteria. Other factors might be taken into consideration: multi-species situation, some specific toxicological requests exists already (MRL's), many of the toxicological considerations are unique to Animal Health, long term human exposure data might be inappropriate, TTC has not been determined for veterinary products.	

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	IFAH-Europe has noticed that no reference to the “Retrospective validation” is done anymore. Any reference to this class of validation has been removed from the general introduction and the specific chapter as well. IFAH-Europe requests to re-integrate the chapter on retrospective validation e.g. after section 4.15.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1.3		**Comment: "**Appropriate oversight" should be defined. **Proposed change (if any):** For clarity reasons, please specify if this "Appropriate oversight" should be performed by QA	
1.5 e) and 1.6		**Comment:** "The VMP…and contain data on at least the following: e) planning and scheduling activities" Validation activities are dependent upon manufacturing schedules which may change frequently. The text should provide flexibility as to how these activities are tracked. **Proposed change (if any):** Please include references to other pharm systems for planning and scheduling. These systems may suffice for tracking and documentation purposes.	
1.5 g)		**Comment:** Not clear what is meant with "handling of acceptance criteria" **Proposed change**: Please define what "handling acceptance criteria" is.	
1.5 i)		**Comment:** The VMP requirements are very prescriptive. Does it need to be so mandated? Why, for example, should it include an assessment of the resources required? **Proposed change**: Please provide a justification for this requirement or otherwise delete it.	
2.2 & 2.9		**Comment:** It is not clear if it is expected that QA will approve/authorise validation documents and/or will make the formal release for the next step in the validation process or who should approve the documentation – see also GMP Chapter 2 for responsibilities of head of QC, head of Production, QA, and QP. **Proposed change:** Please align with GMP Chapter 2 "Personnel"	
Section 3		**Comment:** it should be clarified if it is required to have a formal release between each qualification stages (as described in this section) or only between Qualification and Validation and, Validation and Production? The link between FAT/SAT and IQ/OQ/PQ is not clear. The addition of FAT/SAT activities without further clarification induces the need to conduct 5 successive stages: FAT/SAT/IQ/OQ/PQ. A statement should be added to clarify that §3.6 applies also to IQ/OQ (not only to SAT) and that some of these subsequent activities could also be satisfactorily conducted at this stage.	
3.5		**Comment:** Requirement conflicts with paragraph 3.3, where it is stated that verification of requirements should be performed during DQ prior to FAT. In addition, FAT at vendor should not be required for all	

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		equipment, as discussed in 3.4. **Proposed change (if any):** Please delete paragraph 3.5.	
3.11		**Comment:** It is not clear what the difference is between "maintenance plans" and "preventive maintenance requirements" **Proposed change:** Please change the text to the current Annex 15, sect. 15: ***"The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements."***	
4.4		**Comment:** A bracketing strategy should also be applicable to new products where development data supports no differences among strengths of a common blend, and the process is robust with respect to blending and impact of batch sizes. **Proposed change (if any):** Please revise text to include bracketing strategy for new products when justified as well.	
4.20		**Comment:** Sections e and f appear to be two halves of the same sentence. Typo error.	
4.20		**Comment:** To include a proposed timetable in the mandatory requirements of a validation document, as required by point 4 n) does not add a benefit from quality point of view. There are frequent cases where proposed timetables cannot be kept in process or cleaning validations, because e. g. the product is not manufactured regularly. In projects comprising a prospective validation, like launches of new products, time scheduling is guaranteed by the project management and the target to launch as quick as possible, in concurrent validation projects, the quality is monitored through the number of validation batches required from the specific risk analysis as required by this document. **Proposed change:** Please delete point n) in chapter 4.20	
4.23		**Comment:** Incorrect reference to previous sections (4.1 – 4.15) for continued process verification. The correct reference should be to sections 4.1 – 4.13. **Proposed change (if any):** Please change the reference to sections 4.1 – 4.13	
4.29		**Comment: The r**equirement to address incremental changes is already addressed proactively in 4.28. In addition Section 11 addresses change control; this sentence is redundant and might be confusing. **Proposed change (if any):** Please delete section 4.29	
5.3		**Comment: "**The verification of transportation" should be balanced by the existing data generated during development stage on packaging suitability, stability data…against transportation conditions (humidity,	

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		vibration, handling, delays during transportation, failure of data-loggers, topping up liquid Nitrogen, product susceptibility and any other relevant factors) rather than request to perform a risk assessment systematically.	
5.4		**Comment:** The requirement describes the expectations for transportation of materials, in particular coming into EU or being distributed within EU. For transportation outside EU, a risk based approach in agreement with local requirements of destination markets should be considered for veterinary products. **Proposed change:** Amend text as follows: ***"Due to the variable conditions expected during transport, e.g. delays at airports, continuous monitoring of any critical environmental conditions to which the product may be subjected should be performed. For veterinary products which are being distributed outside of Europe continuous monitoring may not be required, this must be in accordance with local requirements, supported by Quality Risk Assessment and documented."***	
7		**Comment:** The terms "qualification" and "validation" are used interchangeably, are they considered the same? **Proposed change:** Please include the definitions of these words in the glossary and please apply these terms consistently throughout the document.	
8.1		**Comment:** Chapter 6 does not provide the details or describe the way to validate test methods. **Proposed change (if any):** Please include reference to Guideline ICH Q2 (R1).	
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 (if any):** Please modify the text to read **"Where microbial testing of product is carried out, the method should be *demonstrated to be suitable and having the appropriate recovery(*according to EP 2.6.1, 2.6.12 and 2.6.13) *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 for equipment that is disinfected. In addition, it is relative and not an absolute result; the method should be demonstrated to have the appropriate recovery. **Proposed change (if any):** Please modify the text to read **"Where microbial testing of surfaces *is required as part of cleaning verification/ validation exercises, the methods should be***	

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		demonstrated to be suitable and having the appropriate recovery **to confirm that the sanitizing agents do not influence the results."**	
Section 9		**Comment**: Some practical aspects regarding cleaning validation as per described in PIC's guidance are not mentioned: - use of simulating agent - insisting on the product change-over (which seems an interesting precision to be added to the definition).	
9.1		**Comment**: The second sentence: "Where different equipment…" is unclear. Does it refer to equipment train? **Proposed change (if any)**: Please modify the text to clarify the term "different equipment"	
9.5		**Comment**: Last sentence of 1st paragraph: "The removal of any…" Detergents are of multi-components nature but in case of residue determination just a single one is measured. **Proposed change (if any)**: Please remove "any" from this sentence	
9.5		**Comment:** For veterinary products there is a high complexity and high number of dosage forms and species and impact on food chain (if any) and it is very difficult to assess PDE and the cumulative effect of train equipment. Also for veterinary vaccines and other large molecules, the toxicity level is very low (proteins). In addition, a lot of cleaning validation was already performed according to the old approach and it is too complex to repeat cleaning validation studies. Proposal is to keep the old approach for veterinary products and previously accepted limits may continue to apply including the specific exclusions in annex 4. It is noticed that the use of a 10 ppm criterion and/or reference to other toxicologically relevant limits (LD50) is completely omitted. However, in certain cases, the 10 ppm criterion should be kept as a possibility to calculate limits for contamination. In general, limits for residues are regulated in the GMP Guidelines chapters 3.6 and 5. Furthermore, the requirement to use the strictest criterion as acceptance level should be explicitly mentioned. **Proposed change:** Please modify the text to read ***"The limits for the carryover of product residues should be based on a risk assessment taking into consideration toxicological evaluation of the product, specific permitted daily exposure (PDE) value, solubility, cleanability, previous product knowledge, analytical methods used and other factors as considered necessary. The risk assessment and its supporting references should be part of the cleaning validation***	

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		documentation. In case of legacy products, previous knowledge can be used to justify the defined the residuals. **In cases where no PDE is available or applicable (e. g. Ectoparasiticides or substances with very low toxicity), other values like LD 50 can be used or limits can be calculated applying the 10-ppm-criterion. In any case, the stricter limits should apply.** ***Specific exclusions in annex 4 continue to apply for Animal Health."***	
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 (if any):** Please revise text to state ***"...maximum length of a campaign (in time and/or number of batches) should be the basis..."***	
9.8		**Comment:** In analogy to chapter 9.5 we would appreciate to allow for continued use of the 10 ppm criterion in case no other limit is stricter and no PDE or toxicity data are available **Proposed change:** Please add the following phrase to the paragraph: **"The 10-ppm-criterion may apply in cases where no PDE or toxicity data are available and none of the other criteria is leading to lower limits."**	
9.10		**Comment: "***Recovery should be shown to be possible from all materials used in the equipment".* Not all materials may be in direct product contact e.g. some seals or gaskets. **Proposed change (if any):** Please modify the text in order to clarify that recovery studies would be required for all materials of construction <u>in direct contact</u> with the product.	
9.12		**Comment:** Cleaning verification is not defined in glossary; expectations should be defined. Also, Annex reference is not defined. **Proposed change:** Please note the Annex reference in the text and we also recommend cleaning verification be defined in the glossary.	
Glossary / term "Cleaning Validation"		**Comment:** The definition of the term is stricter than the requirements laid out in the corresponding chapter. Moreover, it is not feasible to remove <u>all</u> traces of the previous product. **Proposed change:** IFAH-Europe proposes to use a definition similar to the previous version. **"Cleaning validation is documented evidence that an approved cleaning procedure will remove residues of the previous product to a safe and acceptable level, which does not present a risk to the following product or patient."**	

Please add more rows if needed.