Submission of comments on Revision of ‘Annex 1: Manufacture of Sterile Medicinal Products’

Comments from: NNE, Denmark

Name of organisation or individual
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1. General comments

General comment (if any)

The Annex1 provides a much more detailed explanation of aseptic production areas, technology and processes compared to the current valid guideline.

Suggestion 1: Please specify the requirements for the three options: Aseptic production in conventual classified rooms, RABS and Isolators. The guideline would be more user-friendly if the requirements are listed as:

1. Common requirements for all three options.
2. Specific requirements for the specific chosen technology (for example Isolator)- a section for each possibility (E.g. Differentiated monitoring requirements for conventional clean rooms vs. Barrier technologies)

Suggestion 2:

The expectations on the new Annex 1 was clear statements about “man Away from Product”. We would like to see more emphasize on “man away from product” and not so much emphasize on A/B scenarios

Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
44-48	Comment: The Annex 1 draft describes that QRM principles applies to processes, equipment, facilities and manufacturing with the use of Risk Assessments for justifications to alternative approaches "only if these alternative approaches meet or surpass the intent of this Annex". This poses a risk that authorities will expect that companies surpass the intent and not just meet it. Proposed change (if any): Change wording to: "only if these alternative approaches meet the intent of this Annex"
236-237	Comment: The Annex 1 draft explicit states that no mobile phones should be allowed in clean areas. As the mobile phones are used for communication between different classified and non-classified areas in e.g. emergency situations it should be clearly stated that mobile phones are allowed in CNC/D/C areas. Proposed change (if any): As exception, mobile phones may be used in CNC//D/C areas.
334-338	Comment: That implements that adjacent (in-line) rooms e. g. for container washing, tunnel and vial capping have to be Grade C and not like most common class D. This would be a mayor design impact for all future filling lines in RABS technology.
366-367	Comment: The Annex 1 draft states that the use of separate changing rooms for entering and leaving clean areas is generally desirable. If it becomes mandatory it will be an issue for existing facilities (limited space might make it impossible to fulfil this requirement). For new facilities, it would be acceptable with separate changing rooms. However, when leaving the clean area, it could be satisfactory that you have a common airlock from multiple clean areas. Proposed change (if any): Use separate one direction changing rooms for entering clean areas in new facilities. Leaving clean areas should also be one direction and could be either via separate changing rooms or could be common changing rooms.
505	Comment: Error in last column in table. ISO classification "in operation/at rest"… the values are stated "at rest/in operation"
622	Comment: Correction of spelling error. Proposed change (if any): Change "qualificion" to "qualification" *622 treatment, generation, storage and distribution systems should be subject to qualification,*

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
655-656	Comment: In this general phrase in the draft Annex 1 the requirement is unclear. Furthermore, the typically defined critical parameters of a water system like conductivity, TOC content, endotoxin content etc are already subject to regular trend analysis. Suggested to delete lines 655 to 656. Proposed changes (if any): *Delete lines 655 to 656*
658-660	Comment: Suggested change of wordings in line 658 to 661. Proposed changes (if any): *658 7.5 Current drawings should be available that identify relevant information such as:* *659 throughputs through the pipeline, pipeline slopes, pipeline diameter and shall depict all components like tanks, valves, filters, drains and* *660 sampling points.*
662-663	Comment: Suggested change of wordings in line 662. Proposed changes (if any): *662 7.6 Installation of pipes and ducts and other utilities, located in clean rooms, should allow cleaning and disinfection of outer surface of the pipes.*
672	Comment: *672 7.8 Water for injections (WFI) should be produced from purified water,* This clearly contradicts the Ph.Eur Monograph (0169) which reads: Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water Proposed changes (if any): Align requirement with Ph. Eur.
672-676	Comment: Ph.Eur. already mentions already nanofiltration and ultrafiltration. No need to repeat these requirements. Suggest change of line 672 to 674. Proposed change (if any): *672 7.8 Water for injections (WFI) should be produced from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from* *purified water. It should be stored and distributed* *673 in a manner which prevents microbial growth, for example by constant circulation at a* *674 temperature above 70°C or at a temperature below 10°C.*

678-679	Comment: Suggested change of wordings in line 678 to 679. Proposed change (if any): *678 7.9 Water systems should be validated to prove that their design is able to maintain the appropriate levels of physical,* *679 chemical and microbial control, taking seasonal variation into account.*
681	Comment: Suggested change of wordings in line 681. Proposed change (if any): *681 7.10 Water flow should remain turbulent through the pipes to minimize microbial adhesion.* Add the sentence: *Although the transition from laminar to turbulent flow starts at a low Reynolds number, the Reynols number should be higher than 10000 (ten thousand).*
684	Comment: Strong new requirement. Former practice was 3D rule and drainable systems. How to measure "complete"? Deleted "complete" and change "avoidance" to "minimization". Suggested change of wordings in line 684. Proposed changed (if any): *684 e.g. sloping of piping to provide drainage of all points of the system and the minimization of dead legs. Where*
689	Comment: Change the wording "sterilized" to "sanitized" in line 689. (ref.: please see rational in next comment) Proposed change (if any): *689 the filters should be sanitized, and the integrity of the filter tested before and after use.*
691-696	Comment: Industry does not generally "sterilize" water systems and this is not needed either – they are "sanitized" to control microbial levels. This is not a complete kill as implied by the word "sterilization". USP 1231 advised against use of heat sanitization > 85 degC so the word "sterilization" in this text when referring to heat methods is in conflict with USP 1231 and also with trends in industry to move away from steam "sterilization" and instead towards water sanitization. "Prevent" changed to "minimize", "sterilization" changed to "sanitization", "or regeneration" deleted, "and alert" deleted, "/regeneration" deleted in line 691 to 696. Proposed changed (if any): *691 7.13 To minimize the formation of biofilms, sanitization or disinfection or 692 water systems should be carried out according to a predetermined schedule and also when* *693 microbial counts exceed action limits. Disinfection of a water system with* *694 chemicals should be followed by a validated rinsing procedure. Water should be analyzed* *695 after disinfection; results should be approved before the start of use of the* *696 water system.*

704-706	Comment: The term" each time" in line 705, could be understood as if there should be taken a sample every time the loop is tapped. Normally there are many users with different needs over the day. The requirement of sampling before each tapping from the loop, might indicate the need for a person constantly placed at the sample loop. Proposed changed (if any): *704 specified interval. A sample from the worst case sample point, e.g. the end of the* *705 distribution loop return, should be included daily when the water is used for manufacturing* *706 and manufacturing processes. A breach of an alert limit should trigger review and follow-up,*
706-708	Comment: Recommend putting lines 706 to 708 (dealing with breach of action and alert limits) to a section describing in general validation, action / alert limits. Proposed changes (if any)*706 and manufacturing processes. A breach of an alert limit should trigger review and follow-up,* *707 which might include investigation and corrective action. Any breach of an action limit* *708 should lead to a root cause investigation and risk assessment.*
710-711	Comment: Suggested change of wordings in line 710 to 711 and addition of a sentence to clarify the intent Proposed changes (if any): *710 7.16 WFI distribution systems should include continuous monitoring systems such as Total Organic* *711 Carbon (TOC) and conductivity. WFI generation systems should include continuous monitoring of conductivity.*
715-716	Comment: Feed water to clean steam generators can be currently made (in EU) from water which meets WHO / National standards for drinking water plus any other attributes which the clean steam generators require for feed water (e.g. hardness, silica, conductivity etc). This has been a very successful and cost-effective solution for the water pre-treatment system thus far. Why the need to change? Suggested change of wordings in line 715 to 716. Proposed changes (if any): *715 7.17 Water, that complies with the regulations on water intended for human consumption laid down by competent authority or purified water, should be used as the minimum quality* *716 feed water for the pure steam generator.*

718-723	Comment: Technically, why should a clean steam distribution system should not meet the requirements (perhaps except for NCG): NCG are removed in pre-treatment or in the generator in a defined process step before evaporating. When no requirements for NCG are given, during sterilization of equipment, air (that is contained in the equipment) must be removed before / at sterilization and NCG would be removed as well. There is a permanent flow from steam inlet to condensate outlet. Regarding dryness, at beginning of sterilization, a lot of condensate will occur and is removed to the condensate outlet and additional condensate from steam has a neglectable influence. Regarding superheat, directly after evaporation, the steam is in equilibrium with the water in the generator. There is no further heating, steam cannot be superheated. Furthermore, it condenses in the distribution piping due to heat losses and when it heats up the equipment. Superheated steam (if present at all) gets to the saturation point quickly. Suggest changing line 720 as below and add a sentence after line 724. Proposed changes (if any): *720 quality of steam used for sterilization of porous loads should* *721 be assessed periodically against validated parameters. These parameters should include* *722 consideration of the following examples: non-condensable gases, dryness value (dryness* *723 fraction), superheat and steam condensate quality.* *724 During Steam-In-Place (SIP), remaining gases / air inside the equipment to be sterilized must be adequately removed.*
727-733	Comment: Reference to pharmacopoeia to be deleted. The purpose in the pharmaceutical industry defines the parameters to be specified. When parameter X is not relevant for the purpose, it does not need to be analysed, even it is described in the pharmacopoeia. Points of use filter: it may be part of the distribution system or integrated into the equipment to be supplied with the gas. A failing integrity test indicates that bacteria might have moved through the filter into the product (aseptic manufacturing). So, an integrity test is essential. Suggest changing line 729 and 730 as below and introduce new paragraph. Proposed changes (if any): *727 7.19 Compressed gases that come in direct contact with the product/container primary* *728 surfaces should be of appropriate chemical, particulate and microbiological purity, free from* *729 oil with the correct dew point specification730 . Compressed gases must be filtered through a sterilizing filter* *731 (with a nominal pore size of a maximum of 0.22µm) at the point of use. Where used for* *732 aseptic manufacturing, confirmation of the integrity of the final sterilization gas filter should* *733 be considered as part of the batch release process.* *734 There should be periodic cleaning/disinfection of the vacuum system when there is a risk of contamination of the product.*
745-746	Comment: It is good engineering practice not to ignore defects and to enable supply of cooling as requested. Leakages must be detected and repaired. A leaking system cannot supply sufficient cooling capacity. In addition, when not correctly sized, cooling is not sufficient neither. Suggest deleting paragraph (lines 745 to 746). Proposed changes (if any):
748-749	Comment: If maintenance involves modifications like cutting, welding, changes of the piping system, then leak testing is needed to proof tightness, same is recommended after replacement of components. If piping cooling / systems are in operation, a leak test is not necessary. Suggest deleting paragraph (lines 748 to 749).

	Proposed changes (if any):
751-752	Comment: Background of requirement is unclear. If piping cooling / systems are in operation, the inside of the piping is not accessible. The outer surface of the piping, located in a clean room, is already subject to disinfection when the clean room is disinfectant according to the clean room requirements. Suggest deleting lines 751 to 752. Proposed changes (if any):
815	Comment: *814 Table 4: Examples of operations and which grades they should be performed in* *815* *A Critical processing zone.* *Aseptic assembly of filling equipment.* *Aseptic connections (should be sterilized by steam-in-place whenever feasible).* *Aseptic compounding and mixing.* *Replenishment of sterile product, containers and closures.* *Removal and cooling of items from heat sterilizers.* *Staging and conveying of sterile primary packaging components.* *Aseptic filling, sealing, transfer of open or partially stoppered vials, including interventions.* *Loading and unloading of a lyophilizer* Table 4: Unclear or incorrect statements e.g.: "Removal and cooling of items from heat sterilizers in Grade A"– Not necessary if the goods are sealed "Aseptic connections" – pre-sterilized single use connectors are not steamed-in-place "Staging and conveying of sterile primary packaging components" - Not necessary if the goods are sealed Unloading of a lyophilizer in Grade A is only required if container (e. g. vial complete stopper insertion) is not done as part of the freeze-drying process, should be added in the text or as a note below the table. Or referring to paragraph 8.111 Proposed changes (if any): Clarify the content of this table and specify the condition for loading and unloading of a lyophilizer and refer to paragraph 8.111
899	Comment: *Crimping of vial caps… located at a physically separate station* What about crimping of cartridges? They are normally crimped on the filling line after filling. Here it is a station on the line, but it can be shielded using plexiglass as a partition wall between filling and crimping. Proposed changes (if any):
1167-1169	Comment: *Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected.* This could be interpretated as a requirement to have depyrogenation tunnel which have a sterilizable cooling zone as a feature. Although this is already common industry practice at least for isolator filling lines.

	Proposed change (if any): Clarify that it is *tunnels parts that come into **direct** contact with sterilized components*
1916-1918 and 1882-1883	Comment: *1916 and the level of contamination found in the failed APS. Typically 3 successful consecutive* *1917 repeat APS would be expected; any differences to this expectation should be clearly justified* *1918 prior to repeat performance.* The number 3 - In contradictions with the philosophy of Annex 15, where repetition should be based on QRM Proposed change (if any): Delete reference to three batches or take the wording from Annex 15; " it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process"
2076-2087	Comment: *2076 Clean Non Classified (CNC) area - An area that does not meet any of the formal pre* *2077 determined grades of cleanliness included in the Annex, i.e. grades A to D, but where a* *2078 manufacturer defined level of microbial control is still required. The area should be subject to* *2079 a formal cleaning/disinfection regime and formal environmental monitoring program to* *2080 achieve the defined level of control. The level, type and frequency of both the cleaning* *2081 program and the environmental monitoring program (including contamination limits) should* *2082 be based on a formal risk assessment (captured within the wider contamination control* *2083 strategy) and should be commensurate with the specific risks to the processes and product* *2084 performed manufactured within each CNC area.* *2085* *2086 It is possible that different CNC areas within the same facility may have different approaches* *2087 to control and monitoring, based on differing risks to processes and products.* New requirement to set up a monitoring program in CNC areas as well implementing also to establish limits for viables and non viables. It will impact the flexibility of the facility and what are then the differences between Class D and CNC? Proposed change (if any): Remove the requirement for a monitoring program for CNC