

ANNEX 1: COMMENT SUBMISSION DOCUMENT

Submission Comments on: GMP Annex 1: Proposal for amendments to the environmental classification table for particles and associated text, amendment to section 42 concerning acceptance criteria for media simulations, amendment to section 52 concerning bio-burden monitoring and additional guidance in section 88 on the sealing of vials.

SUBMITTED BY:

REPRESENTING: PARENTERAL DRUG ASSOCIATION

SUMMARY OF COMMENTS RECEIVED

Clause, paragraph, line	Classification C=Critical M=Minor E=Editorial	Comment and rational	Proposed change
Throughout the document.	E	Discontinue the use of the word laminar and/or laminarity. It is generally accepted that laminarity cannot be validated.	Replace laminar with unidirectional.
Clause 4	E	Various sections talk about clean rooms, devices and zones. Comment made to harmonise text.	Label Clause 4 as Clean Zone Classification.
Clause 4	E	Spelling of clean room(s) to be aligned with industry norms.	Change to one word, i.e., cleanroom and cleanrooms.
Clause 4	E	Grade C, in operation, 0.5 um limit is incorrect.	Change from 3 5000 000 to 3 500 000.
Clause 4	C	Classify cleanrooms and clean air devices as per EN ISO 14644-1. EN ISO standard is based on a more rigorous and statistically sound basis.	Modify the table to incorporate non-viable particle counts as per EN ISO 14644-1 or essentially equivalent, e.g., Grade A limit in operation at ≥ 5.0 um could be 20).
Clause 4	C	The section under the table starting with *	Delete the sentence starting with *. The following sentence

ANNEX 1: COMMENT SUBMISSION DOCUMENT

		is contrary to the principles outlined in EN ISO 14644-1. It establishes two limits that conflict with each other.	could be considered: Whilst the maximum permitted number of particles at or greater than 5.0 microns is given as $20/\text{m}^3$, accrual counts should routinely be lower than the maximum. If trend analysis shows a deviation from the norm an investigation/corrective actions should occur. See clause 6.
Clause 4	C	The sentence, “It should be noted that this will give rise to a sampling time of about 35 minutes at each location when using a particle counter with a sample rate of 28.3 litres/minutes (one cubic-foot per minute)., is mathematically correct but it is inaccurate when referencing EN ISO 14644 Classification. To meet EN ISO 14644 requirements for sample volume one must reference equation (B.2) which would require a total sample volume of 20,000 L at a limit of NMT 1 particle at $\geq 5 \text{ um}$.	As noted earlier the classification requirement for NMT 1 particle at $\geq 5 \text{ um}$ should be dropped in favour of 20.
Clause 4	C	Paragraph 3 starting with the “Portable particle counters...” could be misinterpreted to mean that only portable counters should be used in for classification purposes when we believe the intent is that if portable counters are used then a short as possible length of tubing should be used. We have also aligned the wording to EN ISO 14644-3.	Replace with “Particle counters with as short a length of tubing as possible should be used to minimise the loss of ≥ 5.0 micron particles, the transit tube length should not exceed the manufacturer’s recommended length.”
Clause 5	E	Various sections talk about clean rooms, devices and zones. Comment made to	Label Clause 5 as Clean Zone Monitoring.

ANNEX 1: COMMENT SUBMISSION DOCUMENT

		harmonise text.	
Clause 5	E	The use of the word formal in the first sentence and last sentence is unnecessary.	Delete the word “formal”.
Clause 5	C	The recommendation for continuous or frequent sampling in Grade B zones is not justified.	Grade B zones should be subject to routine monitoring, e.g., multiple cubic-foot samples per shift.
Clause 5	C	The requirement: “Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be validated” is not a practical requirement as it is not possible to validate such an installation. It is not possible to compare the installation against a standard.	Whilst the installation cannot be validated it can be qualified to comply with the manufacturer’s instructions. Rewrite the sentence as “The tube from the sample point to the sensor should be as short as possible ensuring the tube length and the radii of any tubing bends does not exceed the manufacturer’s recommendations.
Clause 5	C	It is not possible to comply with the sentence, “The Grade A zone should be monitored at such a frequency that all interventions and other transient events would be captured and alarms triggered in excursions from defined operating norms occur.”, as it is not possible to prove that “ <u>all</u> interventions and transient events” will be captured.	Rewrite the sentence as: The Grade A zone should be monitored for non-viable particles at such a frequency that interventions and other transient events would be captured and trigger an alarm if excursions from normal operating values occurred.
Clause 6	E	Second sentence includes “ $\geq 5. \mu\text{m}$ ”.	Should read “ $\geq 5.0 \mu\text{m}$ may”.
Clause 7	M	The particle limit noted should not be limited to $\geq 5 \mu\text{m}$ particles.	Either rewrite the paragraph to cover “particles $\geq 0.5 \mu\text{m}$ ” or rewrite to read “low levels of particles at the point”.
Clause 47	C	The reference to running a Process Simulation Test per shift is unnecessary. The requirement to capture each employee involved in aseptic operations at least once	Rewrite as: Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). In general, a microbiological growth medium such as soybean casein digest medium should be used. The process simulation

ANNEX 1: COMMENT SUBMISSION DOCUMENT

		per year covers the appropriate requirement. In addition, with modern operating practices it is becoming increasingly difficult to define a “shift”. Another example would be BFS operations where there is, effectively, no shift.	test should imitate as closely as possible the routine aseptic manufacturing process and include all critical manufacturing steps subsequent to final product sterile filtration. The process simulation test should be performed as an initial validation with three consecutive satisfactory process simulation tests per processing line. Normally process simulation tests should be repeated twice per year for each processing line and after any significant modification to the HVAC system, equipment, process and number of shifts. Each person involved in aseptic processing should participate in at least one process simulation test per year. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following recommendations apply: i. When filling fewer than 5,000 units, no contaminated units should be detected. ii. When filling 5,000 to 10,000 units: a. One (1) contaminated unit should result in an investigation, including the consideration of a repeat media fill. b. Two (2) contaminated units are considered cause for revalidation, following an investigation. iii. When filling more than 10,000 units: a. One (1) contaminated unit should result in an investigation. b. Two (2) contaminated units are considered cause
--	--	--	---

ANNEX 1: COMMENT SUBMISSION DOCUMENT

			for revalidation, following an investigation. For any run size, intermittent incidents of microbial contamination in media filled runs can be indicative of a persistent low-level contamination problem that should be investigated.
Clause 57	C	The requirement to perform a bioburden assay on each batch is, under certain circumstances, e.g., double-filtration, unnecessary.	Rewrite the fourth sentence to read “Where duplicate sterilising grade filters are used for aseptic processing or where overkill sterilisation parameters are set for terminally sterilised products the bioburden might be monitored only at suitable scheduled intervals.
Clause 57	M	The phrase “in particular large volume infusion fluids” is unnecessary as this product type is captured under the definition of “all”.	Delete the phrase “in particular large volume infusion fluids”.
Clause 93	C	The requirement to maintain stoppered freeze drying vials under Grade A conditions until capping is unnecessary. Years of product experience demonstrate current industry practices to be acceptable. The requirement for Grade A conditions up to the point of crimping could be counter-productive to good aseptic practice as sterilised aluminium caps would need to be processed, stored and handled in the cleanroom thus leading to more frequent interventions and activity in the controlled environment. The first line in clause 93	Delete the requirement for stoppered freeze drying vials to be under Grade A conditions from the time of partial stoppering to capping. Maintaining the stoppered vials under Grade A conditions is only required until the stoppers have been fully seated. It is the seated stopper that provides the container-closure integrity and not the application of the cap. We would encourage wording similar to that in the FDA guideline “stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be in place to safeguard the product such as local protection until completion of the crimping step. Use of devices for on-line detection of improperly seated stoppers can provide additional

ANNEX 1: COMMENT SUBMISSION DOCUMENT

		covers the requirement, i.e., “Containers should be closed by appropriately validated methods.” Industry has gone to considerable lengths to ensure that stoppers are seated properly, appropriately monitored and protected until the cap has been applied.	assurance.” The practice as recommended in the FDA guide is a well proven internationally accepted practice.
--	--	---	---