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Reference to Correspondence Number – C204656
Proposed <1235> Vaccines for Human Use – General Considerations
USP 41 page 7795

Dear Dr. Saha:

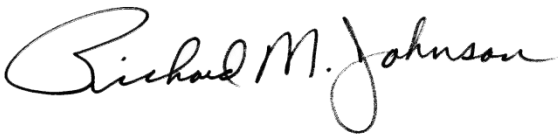
PDA is pleased to have the opportunity to provide comments on the revised USP Informational Chapter <1235>, released for public comment on January 4, 2019. We recognize that the purpose of the proposed revision is to provide guidance on commonalities throughout the vaccine manufacturing process and have provided comments in line with the stated intent.

Our comments were prepared by an international group of expert volunteers with experience in vaccine regulation, development, and manufacture. The following pages present some concerns with the proposed revision overall, as well as a number of technical comments. These specific technical comments are organized by the draft update's section headings.

PDA is a non-profit, international, professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. These comments were prepared by a committee of experts with experience in the practice of pharmacy and pharmaceutical manufacturing including members representing our Board of Directors, our Science Advisory Board, and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President, PDA

CC: Tina Morris, PDA; Joshua Eaton, PDA

PDA Comments on United States Pharmacopeia
⟨1235⟩ Vaccines for Human Use—General Considerations

General Comments

General Comments	Rationale
In Table 2 Vaccine Components, it is not clear why 'materials of animal origin' is listed under manufacturing residuals but not mentioned under protein stabilizers (there is a whole section on animal derived stabilizers later in the document).	It would be good to clarify this distinction.

Specific Comments to the Text

Section	Current Text	Proposed Change	Rationale
Overall Manufacturing Plan	Initial process (production of virus/bacteria and recombinant materials)	Change "initial" process to upstream process. "Upstream process (production of virus/bacteria and recombinant materials)"	More aligned with current industry terminology
Overall Manufacturing Plan	Downstream processes (purification or chemical modification, if applicable)	Change or to and/or "Downstream process (purification and/or chemical modification,"	Both may be used
Overall Manufacturing Plan	none	Add additional bullet line for "Sterility Strategy" * Sterility Strategy (e.g., closed-system process, terminal sterile filtration, bioburden-controlled bulk)	To present a complete plan
Overall Manufacturing Plan	Quality systems are needed to support the following manufacturing process development	Replace with "Quality systems should be developed which govern manufacturing process development, specifications, [continue with list]"	Clarity
Overall Manufacturing Plan	The overall goal of a comprehensive manufacturing program is to consistently and continuously	Remove "and continuously" as it is not always the objective to manufacture continuously	Suggest "...that is safe and effective, while avoiding supply disruptions."
Overall Manufacturing Plan	changes will be required during the vaccine's manufacturing life cycle	Remove "manufacturing" from the phrase "manufacturing life cycle"	Clarity/conciseness
Overall Manufacturing Plan	and failure investigations and complaints	Page 4, reword "failure investigations" Suggest, "deviation investigations and complaints"	More aligned with current industry terminology
Manufacturing Process	Critical process parameters (CCPs)	Change CCPs to CPPs Critical process parameters (CPPs)	Incorrect acronym
Manufacturing Process	The concepts of quality by design and exploration of the process space are…	Delete sentence beginning with: "The concepts of quality by design…"	Unnecessary

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Section	Current Text	Proposed Change	Rationale
Manufacturing Process	unit operations comprising both the initial and downstream processing steps	Change "initial" process to upstream process "… both the upstream and downstream processing steps…"	More aligned with current industry terminology
Manufacturing Process	A process map also supports a processing space to facilitate a rugged process (i.e., one based on suitable characterization studies to establish boundaries within which manufacturing can occur to promote unchanged safety and efficacy outcomes).	Remove this sentence	The last sentence in the first paragraph is ill advised. The process map does not contribute to the ruggedness of the process, the characterization studies do.
Manufacturing Process	The process flow map should include all steps from making the seed/cell bank	The first sentence of the second paragraph is misplaced	Since the subject of the first paragraph is process maps, the first sentence of the second paragraph belongs there, as the third sentence in this (first) paragraph
Manufacturing Process	along with identification of the process space	The term "process space" needs definition.	Suggest "...identification of the process parameter space including associated..."
Raw Materials, Fermentation, and Cell Culture Media (page 6)	A consistent manufacturing process critically depends on the use of consistent raw materials (e.g., during seed banking, propagation, harvest, purification, and formulation). Accurate records of the composition and source of the culture medium used in seed banking and routine fermentation should be maintained, and the release criteria for raw materials or components should also be documented.	Change to: A robust manufacturing process critically depends on the use of consistent raw materials during cell and viral stock seed banking, propagation, harvest, purification, and formulation. Accurate records of the composition and source of the culture medium used in cell and/or viral stock seed banking and routine cell culture or fermentation processes should be maintained. Raw material and media risk assessments and control strategies including release criteria for all components should also be documented and updated throughout the lifecycle of the vaccine.	Clarity

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Section	Current Text	Proposed Change	Rationale
Raw Materials, Fermentation, and Cell Culture Media (page 6)	A medium is the material in which an organism is grown and amplified in quantity to produce mass material for vaccine production. Its composition is diverse and depends on the cell types that the medium supports, ranging from well-defined chemical media to chemically undefined media that contain natural components such as sera from animal origin (see Bovine Serum ⟨1024⟩).	Change to: A medium is the material in which an organism is grown and amplified in quantity to produce mass material for vaccine drug substance production. Media compositions can be diverse and are dependent on both the cell type as well as the nature of the drug substance (i.e. recombinant proteins, polysaccharides, virus, etc.). Cell culture media can range from a well-defined chemical composition to chemically undefined media containing natural derived components such as sera from animal origin (see Bovine Serum ⟨1024⟩).	Clarity
Raw Materials, Fermentation, and Cell Culture Media (page 6)	Manufacturers should consider the source of each of these raw materials to ensure that they come from reliable vendors who adhere to cGMP quality standards and can assure a long-term supply.	Manufacturers should consider the source of each of these raw materials to ensure that they come from reliable suppliers as approved by the Quality Unit, taking into account fit-for-use quality standards. Manufacturers should establish change control agreements with their suppliers to ensure visibility to changes.	Clarity/best practice
Raw Materials, Fermentation, and Cell Culture Media (page 6)	Consistent raw materials are particularly critical for more complex fermentation components such as fetal calf serum, yeast extracts, or peptones, for which changes may be difficult to detect but are likely to have a direct effect on fermentation.	Maintaining the qualified status of the raw materials (taking into account inherent variability) are particularly critical for more complex media raw materials such as fetal calf serum, yeast extracts, or peptones, for which changes may be difficult to detect but are likely to have a direct effect on process performance.	Clarity
Raw Materials, Fermentation, and Cell Culture Media (page 6)	culture medium used in seed banking and routine fermentation	Update wording on "seed banking" Should include "cell or virus seed banking"	Reflect current practices

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Section	Current Text	Proposed Change	Rationale
Raw Materials, Fermentation, and Cell Culture Media (page 7)	The use of antibiotics should be minimal or should be avoided to ensure that no unwanted antibiotics are included in the drug product unless they are intentionally used in manufacturing (e.g., as selective markers).	The use of antibiotics should be minimized if they are required for drug substance manufacture (e.g., as selective markers) or fully eliminated to ensure that no unwanted antibiotics are included in the final drug product.	Clarity
Raw Materials, Fermentation, and Cell Culture Media (page 7)	As manufacturers scale up fermentation to pilot production (i.e., within 10-fold of final manufacturing scale), they should also ensure, to the extent possible, the...	Change "fermentation" to "processes"	Clarity
Raw Materials, Fermentation, and Cell Culture Media – Materials of Animal Origin (page 7)	If additives from animal sources are added to the culture medium, they should be certified to be free from contaminants and adventitious agents, or raw materials should be sourced from countries acceptable to the FDA.	If additives from animal sources are added to the vaccine manufacturing process, they should be assessed with respect to contaminants and adventitious agents. For ruminant raw materials, further assessment of BSE/TSE risk includes sourcing from acceptable countries.	Clarity

Section	Current Text	Proposed Change	Rationale
Raw Materials, Fermentation, and Cell Culture Media (page 7)	Additionally, manufacturers should test these materials when possible to minimize the risks of contamination with adventitious agents, such as those that cause bovine spongiform encephalopathy or transmissible spongiform encephalopathy (TSE).	Additionally, manufacturers should test these materials when possible to minimize the risks of contamination with adventitious agents, where possible.	Clarity
Propagation and Harvest (page 7)	...initiation of cell growth in the working cell bank to the separation...	Change to...initiation of cell growth from the working cell bank to the separation...	Clarity

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Section	Current Text	Proposed Change	Rationale
Raw Materials, Fermentation, and Cell Culture Media (page 7)	As manufacturers scale up fermentation to pilot production	Suggest revising to "as manufacturers scale up fermentation and cell culture to pilot production"	Clarity
Sterile Filtered Bulk (pg 9)	However, the currently used 0.22-µm sterile filter membranes…	Change reference to "0.2 µm"	References "0.22 µm" filtration. Millipore is the only filter manufacturer that claims 0.22 µm. Most other filter manufacturers claim "0.2 µm" pore size, which is the industry standard.
Sterile Filtered Bulk (pg 9)	The final step in the manufacturing of antigen intermediates is the preparation of sterile filtered bulk	Change "is" in first line to "often includes"	Clarity
Sterile Filtered Bulk (pg 9)	solution containing bioburden of a high concentration of at least 10^7 colony forming units (cfu)/cm	Suggest to specify the organism (*B. diminuta*) that is used in filter validation	The sentences on filter validation states 'remove microorganisms from a carrier solution … at least 10^7 CFU/CM2'. Filter validation typically demonstrates removal of a standard test organism (*Brevundimonas diminuta*), instead of a panel of organisms.
Sterile Filtered Bulk (pg 9)	(unpublished company results for 0.22-µm polyvinylidene fluoride membranes demonstrated that a bacterial challenge concentration as high as 10^9 cfu/cm can be validated)	Propose to remove this sentence.	Uncertain of the purpose of citing unpublished company results of challenge concentration of 10^9 CFU/cm2. The point of this section is to say that filters used for sterile filtration of the bulk must be validated. This sentence does not add any value to the point of this section and therefore is not needed.

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Section	Current Text	Proposed Change	Rationale
Final Bulk (page 9)	Current section	Propose to clarify	Addition of diluents, excipients, etc. can happen before the bulk is sterile filtered, provided that the formulated bulk is then sterile filtered before filling. The current wording gives the perception that the sterile filtered bulk steps comes before the production of final bulk. It's not always the case.
Stability test for final bulk (page 9)	If final bulks are stored and/or subsequently shipped to a different location for…	Propose to clarify	The formulated bulk is not always sterilized if the bulk is stored and shipped to a DP facility for filling. The final filtration step can happen (and should happen) immediately prior to filling. In these cases, the stability testing should include bioburden and/or endotoxin
Production of Final Bulk (pg 9)	addition of diluents, bulking agents, stabilizing excipients	remove 'bulking agents'	that is for small molecules not vaccines
Final Container; Stabilizers (pg 10)		Indicates gelatin and HSA are the only proteins approved for use as stabilizers. Other proteins are currently being used as novel excipients for vaccines.	Add rHA or indicate The particular materials chosen for this purpose include (but not restrictive to) sugars….
Stabilizers (page 10)	The primary purpose of stabilizers is to protect certain vaccines from adverse conditions such as heat or to serve as a cryopreservative during the lyophilization process, usually during the freezing step.	Change to "The primary purpose of stabilizers is to maintain effectiveness of the vaccine during processing and storage. Stabilizers can protect vaccines from adverse conditions such as heat, oxidative stress, and changes in pH. They also can serve as cryoprotectants or lyoprotectants during the freezing and drying steps of lyophilization." Change suggested because current wording seems too narrow.	Clarity

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Section	Current Text	Proposed Change	Rationale
Stabilizers (page 10)	The particular materials chosen for this purpose include sugars (e.g., sucrose or lactose), amino acids [e.g., glycine or glutamic acid (monosodium salt)], glycerol, and proteins [e.g., human serum albumin (HSA) or gelatin].	Change "glycerol" to "sugar alcohols" to encompass more stabilizers, such as sorbitol, in addition to glycerol.	Clarity
Adjuvants (pg 10)	Adjuvants - section on drug product	there are some potentially novel adjuvants discussed here, include regulatory reference	Clarity
Final Container - stabilizers (pg 10)	At present, two proteins are used as stabilizers for vaccines: HSA and gelatin.	At present, two **common** proteins are used as stabilizers for vaccines: HSA and gelatin.	Clarity/other proteins are used
Final Container - stabilizers (pg 10)	Gelatin or processed gelatin also is used as a vaccine stabilizer. The gelatin source may be either bovine or porcine. Although the conditions of manufacturing … material to demonstrate that it is TSE-free.	Move to animal origin section	this should be in the animal origin section, not added here. It doesn't make sense to do it twice. (also, you can't test for TSE)
Manufacturing residuals (pg 10)	Therefore, the goal is to reduce these substances to an undetectable level,	If applicable, the goal is to reduce these substances to an undetectable level,	Substances may not be present
Cell-derived residuals (pg 10 - 11)	In the case of gram-positive bacterial vaccines, the endotoxin testing should be conducted to ensure that no contaminants from gram-negative bacterial growth are present.	Suggest to change from “should be conducted” to “should be considered”	Although testing for endotoxin will serve as both a "purity" and "safety" measure (gram negative do produce LPS), the probability is low for LPS
Cell-derived residuals (pg 10 - 11)	In the case of live viral vaccines, considerations may be given to the reduction of cellular residual materials (e.g., host DNA, proteins).	Move this sentence to the first paragraph	this sentence seems to be in the wrong spot
Stability Protocols (pg 11)	Section	Add: Another use of stability data/rate is to determine release potency specifications to ensure that Drug Product will meet end-expiry potency specifications, i.e. development of a release model.	Completeness
Container (Page 12)	Vial/syringe material is typically USP Type I borosilicate glass	Remove reference to USP Type 1 Borosilicate glass	Recommend to not specify Borosilicate as this will eliminate future alternatives

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Section	Current Text	Proposed Change	Rationale
Container (Page 12)	treated to prevent delamination (spalling)	Remove this sentence as we are no longer using treated glass...	appears to specify treated glass to prevent delamination
Lot Release Testing - General Principles	The lot release protocol for each vaccine includes the specific potency test, as well as common tests, such as the visual inspection of final vials, and safety, sterility, and purity testing for each lot.	Remove “visual inspection of final vials”	Release protocols **DO NOT** include visual inspection information of final vials. This information is provided as part of a COA that are issued as part of lot release. Although the statement indicates "such as", would suggest removing this as focus is on Safety, Purity and Potency of vaccine products.
Glossary	Validation: The performance characteristics…	Replace the existing definition of "Validation" with the ICH Q7 definition Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria. (Reference ICH Q7)	Globally accepted
Glossary	Adventitious Agent: microorganism	Change microorganism to entity	It is more than just microorganism (e.g. prion)
Glossary	Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.	Remove the definition component. add the following instead: Ancillary Raw Material: Excipient: Residual: Impurity:	Completeness