

Nancy Kavanaugh PhD, Point of Contact, Regulatory Affairs Vaccines

Concern	Suggested revision (if applicable)	Section
<p>The introduction indicates that the purpose of the document is to provide guidance on cell substrates and viral seeds. In addition the document title uses the term "biological starting materials" yet no definition is supplied in the text or glossary to define a starting material" this needs to be remedied.</p> <p>Need to introduce and define product "intermediates" as distinct form starting materials in text and glossary.</p>	<p>Define "starting material" and further refine for interested "biological starting materials". Need to include MVS, WVS, MCB, MWCB, recombinant plasmids, etc.</p>	<p>I (Introduction)</p>
<p>Introduce term "raw materials" but no definition provided in text or glossary. Need distinction for biological raw materials versus raw materials of non animal origin.</p>	<p>Define raw materials, and distinguish biological versus raw materials of non-animal origin. Distinguish a raw material from starting material.</p>	<p>II.B.1 (Vaccine Purity)</p>
<p>This is contrary to the experience of MedImmune. MedImmune requested an opportunity to discuss our characterization approach for a cell substrate and are meeting request was refused verbally and in writing.</p>	<p>Please define "feasible" and provide the mechanism for regulatory meetings to discuss this and other proposed methodology and validations associated with the characterization and qualification of cell substrates for the production of viral vaccines.</p>	<p>II.B.1 (Vaccine Purity)</p>
	<p>Change section title to reflect biological starting materials or use subsections based on each starting material.</p>	<p>II.B.2 (Potential Sources of Contamination)</p>
<p>Use of Control-Cell Cultures is ambiguous as a reference to manufacturing of seeds vs. bulks. Needs clarification.</p> <p>Also conflicts with EP requirements, as prescribed in 2.6.16 "Tests For Extraneous Agents In Viral Vaccines For Human Use," there is a requirement for assessing control cell cultures. Introduction suggests ICH harmonization is one reason for the document.</p>	<p>Need to clarify application of guidance to production lots, and clarify starting materials vs. product intermediates, vs. drug product manufacturing.</p>	<p>II.B.4 (Use of Control-Cell Cultures)</p>
<p>Vaccine Production is introduced in the section title, yet this was not the original intent. If it is , the document needs to be revised to include not only starting materials but also bulk vaccine manufacturing.</p>	<p>Need to clarify application of guidance to production lots, and clarify starting materials vs. product intermediates, vs. drug product manufacturing.</p>	<p>V. (Characterization and Qualification...)</p>
<p>Again vaccine production is discussed and further clarification of document purpose: "we do not generally recommend that sponsors assess virus production lot-by-lot for human papillomaviruses once the initial cell substrate and viral seed have been demonstrated to be free of these agents".</p>	<p>Need to clarify application of guidance to production lots, and clarify starting materials vs. product intermediates, vs. drug product manufacturing.</p>	<p>V.A.5. (Susceptibility to Adventitious Agents)</p>
<p>The text is somewhat misleading for those without a historical understanding of the removed 21 CFR 630 regulations. If reference is being made to support the applicability of the concepts, it should be noted that they were applicable to only limited specific licensed vaccine products. If the reference is not going to be accurate as to applicability, we would argue that the reference to 21 CFR 630 regulations should be removed from the guidance document in all occurrences.</p>	<p>Recommend revision to read "Many of the tests in tissue culture or animals were originally promulgated in 21 CFR part 630 <i>as being applicable to only specific licensed viral vaccines and never considered to be global requirements for all viral vaccines. These remained in the regulations until revision of the regulations in 1996.."</i></p>	<p>V.B.1 (Qualification of Cell Banks and Primary Cells)</p>

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<p>A point to note is CBER's continued interest in neurovirulence testing. "Assessment of neurovirulence is often appropriate, and we recommend that you consult with CBER on appropriate animal models, methods, and scoring systems for this assessment before you initiate such studies."</p>		
<p>Section Discusses extraneous agent testing of bulk harvests. Needs clarification as this material is not a starting material, rather an intermediate or potentially a drug substance.</p>	<p>Need to clarify application of guidance to production lots, and clarify starting materials vs. product intermediates, vs. drug product manufacturing.</p>	<p>V.C.0. (Master Viral Seed)</p>
<p>Control cells are referenced.</p>		<p>V.E. (Considerations in Testing At Different...)</p>
<p>Typographical error in first sentence of second paragraph - "he" should read "the"</p>	<p>Correct spelling</p>	<p>V.E.2. (Pre-Filter Harvest...)</p>
<p>Use of the phrase "Quality Control Test Methods" in this section may lead some readers to believe that this is a requirement for routine in-process controls of commercial product. See 21 CFR 211.160(b) for one potential source of confusion relative to routine in-process testing in use of the term "controls."</p>	<p>Please consider revising to replace use of the phrase "quality control" throughout the document with the phrase "test methods" or "characterization methods."</p>	<p>VI. (Description of Quality Control...)</p>
<p>The text is somewhat misleading for those without a historical understanding of the removed 21 CFR 630 regulations. If reference is being made to support the applicability of the concepts, it should be noted that they were applicable to only limited specific licensed vaccine products. If the reference is not going to be accurate as to applicability, we would argue that the reference to 21 CFR 630 regulations should be removed from the guidance document in all occurrences.</p>	<p>Recommend revision to read "Many of the recommended test described later in this document were originally promulgated in 21 CFR part 630 <i>as being applicable to only specific licensed viral vaccines and never considered to be global requirements for all viral vaccines. These regulations were revised in 1996...</i>"</p>	<p>VI.A. (Testing for Adventitious Agents) - Second paragraph</p>
<p>A conservative read of this section may lead one to believe that these tests are universally required. We recommend being more explicit on this point by revised the wording as suggested in the following. The suggested revision is consistent with the policy stated in the section II.A.2nd paragraph noting that characterization and qualification activities for cell substrates may be sufficient to support waiver of performing certain types of routine tests to meet release requirements.</p>	<p>Please consider adding another sentence at the beginning of the third paragraph of section VI.A. as follows: "Not all of the tests described in the section will be required in all circumstances. The appropriate tests for adventitious agents will vary depending on a variety of factors, including the original of the cell substrate and its history."</p>	<p>VI.A. (Testing for Adventitious Agents) - Third paragraph</p>
<p>"Each lot of product harvest concentrate should be tested prior to further processing, e.g., prior to clarification, filtration, purification, and inactivation, unless testing at this stage of the manufacturing process is not feasible."</p>	<p>Need to clarify.</p>	
<p>I assume that this should read...Each lot of product harvest concentrate should be "sampled for testing without " further processing... I believe that manufacturers do not need to wait for the testing of the material before performing downstream processing, particularly if it is straight through processing.</p>		<p>VI.A.2 (In Vitro tests for Non-Viral Agents)</p>
<p>Recommended dosing of 0.100 mL for newborn mice is high. The largest dose we have seen a IUCAC allow would be 0.050 mL.</p>	<p>Reconsider practicality of dose volume for newborn mice. Recommended volume is high relative to stress to newborn mice.</p>	<p>VI.B.0 (Tests for Tumorigenicity)</p>