<table>
<tr><th>Section</th><th>Line/Paragraph</th><th>Current Wording</th><th>Suggested Change (revised wording)</th><th>Comment/Rationale/Reason for Change</th><th>Critical/ Major/ Minor/ Editorial</th></tr>
<tr><td>NA</td><td>General Comment</td><td colspan="3">Industry feels it would be appropriate for FDA to specify its requirements and expectations for mycoplasma testing in separate guidance so that information can be easily identified (versus only included in copious text of various guidance documents).</td><td>Minor</td></tr>
<tr><td>NA</td><td>General Comments</td><td colspan="3">The document often does not make a distinction between tests / study designs for which the intended test articles are cell banks or cells used in production and tests / study designs for which the intended test articles are harvest or bulk materials. For any given stage of manufacturing, this lack of clarity can lead manufacturers to perform testing that is not scientifically justifiable, which in turn can result in delays in development and manufacturing, as well as an inappropriate data package for FDA review. Distinctions should be made in the description of each stage with respect to which testing is required and to which products the tests apply. Integration of specific examples would also be helpful in this regard.

Additionally, the document does not appear to make a distinction between testing required for recombinant subunit vaccines, which are highly purified and included in the ICH documents, and vaccines which are excluded from the scope statements for these documents. This apparent lack can lead to some confusion on the part of manufacturers who wish to submit regulatory filings both within and outside the United States.</td><td>Major</td></tr>
<tr><td></td><td>General Comment</td><td colspan="3">The term “might” is used consistently throughout the draft (106 times) which seems an unprecedented usage for what can be an ambiguous term. While the industry acknowledges and fully appreciates that this is a guidance document and therefore by nature is written to allow the sponsor a certain level of flexibility in approach (based on evolving science and technology), additional detail regarding specific FDA expectations and requirements, where applicable would be appreciated. In this regard, rather than using the word “might” in all cases, it would be helpful to have additional examples of situations where sponsors should</td><td>Major</td></tr>
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Section	Line/Paragraph	Current Wording	Suggested Change (revised wording)	Comment/Rationale/Reason for Change	Critical/ Major/ Minor/ Editorial
		consider particular testing using specific materials or methodology(s) at various manufacturing and testing points.			
I	§ 3, sentence 2 General Comment	The scope statement for ICH Q5A specifically excludes inactivated vaccines and all live vaccines containing self-replicating agents; only recombinant subunit vaccines are included. In general, it is apparent that there are instances of inconsistency between this Draft Guidance and previous documents that have been issued since the 1993 Points to Consider, such as ICH Q5A, and Q5D. In the spirit of harmonization, FDA should reconcile the information in this Draft Guidance with those documents where applicable. Furthermore, as this document only addresses starting materials for viral vaccines, the Industry requests an update of the 1993 Points to Consider to focus on products that were included in the 1993 document but are outside the scopes of both the ICH documents and this new guidance.			Major
II. A.	§2	…and potential oncogenic agents	…and potential oncogenic virus(es)	Oncogenic agents is a too broad a term; virus should be specified.	Major
II.A	§4, last sentence	"In some situations, additional validation studies to demonstrate…"	"In some situations, additional studies to demonstrate…"	This is a misnomer, in that actual clearance studies are not validated, the readout assays are..	Major
II.B.1	§ 1, last sentence	"…vaccines to validate clearance of any adventitious agent	" vaccines to demonstrate clearance of adventitious agents."	This is a challenge of process capabilities, not a validation exercise.	Major
II.B.1	§ 2, first sentence	"…more reliance on process validation	"…more reliance on the clearance capacity of the	ICH Q5A (Ref 2) does not discuss process validation,	Major

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		(Ref. 2)."	manufacturing process (Ref. 2)."	nor does it infer that a determination of viral clearance is part of process validation. Initial studies performed to support the use of the product in phase 1 clinical trial use materials from processes that are not yet validated. References to validation throughout this section should be rewritten to reflect process challenge and process capabilities (see comments previous and just following this comment).	
II.B.1,	§ 2, third sentence	"…provide documentation of your validation…"	"…provide data to support your claim for inactivation…"	This is a challenge of process potential, not a validation exercise.	Major
II.B.1	§ 3, first sentence	"…vaccine including starting materials used…"	"…vaccine, including those used to treat the starting materials, as the…"		Minor
II. B. 1. Vaccine purity	§4	(e.g., by molecular cloning, serial passage….)	(e.g., by molecular cloning using end-point dilution, serial passage…).	Technique for efficient cloning	Minor
II. B.2.	§ 1	Testing might be	Testing might be needed	The testing should be limited	Major

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Potential Sources of Contamination		needed to verify the absence of additional contaminating agents, particularly those agents whose propagation might be supported by your cell substrate	to verify the absence of additional contaminating agents, particularly those agents that are human pathogens whose propagation given their passage history might be supported by your cell substrate	to the relevant agents that are known pathogens for humans and that could be found as contaminants given the passage history.	
II.B.3	First & second sentence		Delete reference to 21 CFR part 58	The GLP regulations are specific for safety testing	Minor
III.B.4 Use of Control-Cell Cultures	§ 1, third sentence	"…presence of adventitious agents by direct observation and testing of the cell sheet and…"	"…presence of adventitious agents by direct observation, and testing of the cell sheet and…"	Clarity	Editorial
II.B.4. Use of Control-Cell Cultures	§ 1 + § 2	If you are using primary cell culture to propagate your virus...In this situation, you should produce and test uninfected control-cell cultures…Use of control-cell cultures is important when your vaccine might interfere	-	It appears that that control cells are only required when primary cell cultures are used for production or when the product interferes in the test system and cannot easily be neutralized to enable testing for extraneous agents. This should be further clarified in the text, accordingly.	Comment

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		with results of in-process testing of the product; for example when the virus cannot easily be neutralized to permit testing for adventitious agents			
II.B.4. Use of Control-Cell Cultures	§ 1 + § 2	"You should produce and test uninfected control-cell cultures that are derived in parallel with and handled in the same manner as the production culture".	"You should produce and test uninfected control-cell cultures that are derived in parallel with and handled in the same manner whenever and wherever possible as the production culture. Alternative culture conditions may be implemented if justified.	In some instances, control cells cannot be handled exactly in the same way as production culture (see examples in next comment).	Major
II.B.4. Use of Control-Cell Cultures	§ 2	"You should use a culture period of at least 14 days…"	You should use a culture period longer that the period used for the production of the viral harvest and, if applicable, at least 14 days. Alternative periods (because of the cell nature) may be	For example, for some cells cultured in suspension (e.g. Hi-5, CHO) , it is impossible to maintain the cells for a long periods of time without subculture. Therefore, by default, the handling of the cells will not be identical to that applied for the production	Critical

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			appropriate.	cells.	
II.B.4. Use of Control-Cell Cultures	§ 2	"Testing of control cells does not always eliminate the need for testing end-of-production cells, which might be required to demonstrate the absence of agents induced during vaccine manufacture."	"Testing of control cells does not always eliminate the need for testing end-of-production cells, which might be required to demonstrate the absence of agents induced during vaccine manufacture. These end-of-production cells might be tested during the validation of the MCB or the WCB."	Provide clarity on the normal/appropriate time during product development for testing of EOPC and allow flexibility to not test routinely (per other guidance). Please provide an example of circumstances under which a sponsor would be required to routinely test the EOPC during production.	Minor
III.A.1	§ 4,first sentence	"Whatever starting materials are used for generation of the cell substrate…"	"For each starting material (e.g. cells, plasmids) that contribute to the generation of the cell substrate, complete information including characterization should be provided."	Clarity	Editorial
III.A.1	§ 4,last sentence	See Sections III.A.2. for ….. on donor sceeening.'	See Sections III.A.2. through III.A.7. for additional information.'		Editorial
III.A.2	sixth sentence	'Issues ... are dicussed in ..'	'Issues .. discussed in ..'		
III.A.3	§ first sentence	'.. adherence to GLPs	'..adherence to cGMPs	The GLP regulations are	Minor

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		or cGMPs ..'	..'	specific for safety testing	
III.A.3. History	§ 2	"listing of any other agents grown in the facilities around the time of cell substrate passage"....."You should provide documentation of all raw materials you used for the entire passage history"	"listing if available of any other agents grown in the production unit around the time of cell substrate passage"....."You should provide all documentation available for all raw materials from human or animal origin that you used for the entire passage history"	Change to narrow to the production unit (more relevant than larger facility). In some instances, the level of documented historical detail may be limited; therefore sponsor should be required to provide as much information as is practically available. Should be considered that certain Cell Banks or certain Virus Seeds are developed by parties other than the sponsor, e.g. in University laboratories.	Minor
III.A.3. History	§ 2	You should also provide the following: age, gender, and species of the donor; donor's medical history and results of tests performed on the donor for the detection of adventitious agents ….	You should also provide the following: donor's medical history and results of tests performed on the donor for the detection of adventitious agents…introduced into the cell substrate. For instances in which the specified information is not available (eg. donor	Medical history of the donor is not always available; acknowledgement of potential inability to provide comprehensive medical information on the donor (and therefore to supplement with other information) is also in harmony with requirements of ICH. The same comment applies to the other items in this bullet list.	Minor

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			medical history), data derived from analysis of the substrate by other methods may prove supportive and may be required.		
III.A.4. Growth Characteristics	§ 1	"You should perform tumorogenicity testing on continuous cell lines. A description of the tumorigenic property of the cells is required for all diploid and non-diploid cells…"	"Per 21 CFR 610.18(C)(1)(ii), a description of the tumorigenic property of the cells is required for all diploid and non-diploid cells. However, the requirements in this regulation are not applicable to diploid cell strains that are not genetically modified and are not novel, such as MRC-5, WI-38 and FRhl-2, as they are extensively characterized and well-defined, and their non-tumorogenic phenotype satisfies these CFR requirements (see also section III.B.4 of this	Provides consistency with Draft Guidance Section *III.B.4. Special consideration for diploid cells* where it is mentioned that animal tumorigenicity testing is not needed if you are using genetically unmodified diploid cell strains such as MRC-5 and WI-38 and FRhl-2, because their extensive previous characterization and well-defined non-tumorigenic phenotype satisfies the requirement in 21 CFR 610.18.	Major

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			guidance)…”		
III. A.5. Expression Characteristics	§ 1	“If viral sequences are related to the expression system, you might need to assess their infectivity and potential interference with adventitious agents testing.”	-	Please define what is meant by viral sequence	Comment
III. A. 5 Expression Characteristics	§ 5	“In some cases…to evaluate expression of other genes relevant for cell phenotype.”	-	It would be helpful to have Specific examples of when this should be performed	Comment
III. A. 6 Susceptibility to adventitious agents	§ 1	“For example, specific tests were required to assay for these viruses in each lot ..;”	“If viruses were detected in the cells used for production, lot to lot testing should be put in place. “	It is not practical or feasible to implement testing for all possible contaminants on a routine lot-to-lot basis; therefore lot-to-lot testing should be implemented, as necessary, based on agents identified during characterization of the cell substrate.	Major
III.A.7 Generation of Cell Substrates	§ 1	“In addition, a cell substrate that has been derived by cell cloning might have different characteristics from	-	It should be clarified if a well-characterized cell line that is grown in a new culture medium is considered as a new cellular substrate that	Comment

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		the parenteral cell line. Because it is derived from one or a few cells, it might not have characteristics representative of the original population from which it was cloned."		needs full characterization.	
III.B.1	§ 1 &2 (and glossary)			The definitions for the Master Cell Bank and the Working Cell Bank are inconsistent with those in ICH Q5A / Q5D. The MWCB does not exist in ICH documents.	Minor
III.B.1	§ 4, second sentence		' .. should be completely characterized and the choice of that test point should be justified.'	Without inclusion of a rationale for the choice of test point, this instruction is too open-ended to be meaningful.	Minor
III. B.2. Qualification of Cell Banks and Primary Cells	§ 2	"Testing to qualify the MCB should be performed directly on the cell bank, except when it is more appropriate to test cell cultures derived from the cell bank"	"Testing to qualify the MCB should be performed directly on the cell bank, except when it is more appropriate to test cell cultures derived from the cell bank or when the MCB amounts are	Other than a filtration based test for bacteria and fungi, it is not feasible to perform tests for mycoplasma or viruses on cells directly from the cell bank ampoules for at least three reasons: (1) the cryoprotectant in the freeze medium will interfere with a	Minor

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			too limited.”	number of the tests; (2) the tests should be performed on cells in their culture media; and (3) too many ampoules of the MCB would need to be used to complete the testing.	
III.B.2 / p 12	§ 4, first sentence	‘Either the MCB or all animal-derived reagents ..’	‘The MCB and all animal-derived reagents to which it has been exposed should be shown ..’	This sentence implies that complete testing of reagents can substitute for some of the testing on the MCB, and does not take into account the potential for amplification of low level contaminants while expanding the culture to generate sufficient cells for banking.	Minor
III.B.5 / p 14 III.B.7 / p 15	Paragraph 4		Substitute ICH terminology for ‘end of production’ and ‘EOPC’	Consistency with internationally accepted terminology	Editorial
III. B. 7. End-of-Production Cells	Last sentence	“Your characterization should include,…stability of expression of the inserted or engineered genes and genetic stability”	“Your characterization should include,…stability of expression of the inserted or engineered genes and genetic stability, if applicable”	Add “if applicable” at the end of the sentence as this should be applicable for genetically modified cell substrates.	Minor
III.C.1. Master Viral Seed	§ 2	“Viral seeds should be stored in liquid	“Viral seeds should be stored in liquid nitrogen	The working Seeds can also be stored at -70°C	Major

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		nitrogen and in more than one location….”	or at -70°C and in more than one location….”		
III.C.1. Master Viral Seed	§ 1	“You should perform tests for identity (which could necessitate sequencing the entire vaccine virus)”	You should perform tests for identity (which could necessitate sequencing the entire vaccine virus or the relevant part of the live attenuated vaccine virus.	It should be clarified in which circumstances the identity of the virus seed lots requires sequencing of the entire genome in case of live attenuated virus.	Minor
III.C.1. Master Viral Seed	§ 4	“Assessment of neurovirulence is often appropriate, and we recommend that you consult with CBER on appropiate models, methods, and scoring systems.”	“Assessment of neurovirulence might be appropriate, and we recommend that you consult with CBER on appropriate models, methods, and scoring systems.”	Change from “often” to “might”. This is an instance where the use of the term “might” or “may” provides the sponsor with appropriate flexibility to accommodate current science. In recent discussions in the scientific community it was suggested that the potential neurovirulence of the vaccine strain should rather be considered during preclinical development, based on available data, notably for wild type virus or based on results from test carried out on the vaccine strain using an animal model that	Major

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				differentiates wild type and attenuated virus. The requirements for neurovirulence testing of the Working Seeds were reviewed at a joint EDQM-WHO-IABS scientific workshop. Ph. Eur. Monographs for all live attenuated vaccines were reviewed according to the conclusions of this meeting. Except for the oral poliomyelitis vaccine, the routine test of neurovirulence for all the other live attenuated Virus Seeds will be suppressed in the Ph. Eur.	
III. C. 2. Working Viral Seed	§ 1	" You may subject the Working Virus Seeds (WVSs) to less rigorous characterization than the MVSs from which they were derived."	" You may subject the Working Virus Seeds (WVSs) to less rigorous characterization than the MVSs from which they were derived. Alternatively, some manufacturers may choose to extensively	Like for the Cell Bank extensive testing should be allowed on the Master Viral Seeds or on the Working Viral Seeds given the limited amount of Master Viral Seeds. The testing of the MVS will be a one-time testing.	Major

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			characterize each WVS in lieu of thorough characterization of the MCB.”		
III.D. / p 18	§ 2	‘..are discussed in Section III.’	‘..are discussed below and in Section IV.’	To include sections referenced in D1 – 4.	Editorial
III. E. Considerations in testing at different stages of production	§ 2. Pre-production cells	2. Pre-production cells: an identity may be performed on cells directly prior to production	3. Pre-production cells: an identity may be performed on cells used for production		Minor
III.E. 3. Pre-Filtered Harvest or End-of-Production Cells	§ 2	“ In addition to testing he viral or vaccine bulk for cultivatable mycoplasma …. And adventitious viruses by in vitro and in vivo methods.”	“ In addition to testing the viral or vaccine bulk for cultivatable mycoplasma …. And adventitious viruses by in vitro methods.”	The purpose of testing the downstream manufacturing stages is to assess any potential for contamination that may have occurred during the manufacturing process (and therefore, adherence to GMPs). This can be appropriately and specifically accomplished by employing the in vitro viral screening method alone. The utility of the burdensome in vivo method at this juncture in the	Critical

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				process is questionable. Typo – add “t” to “he”	
III.E. 3. Pre-Filtered Harvest or End-of-Production Cells	§4, last sentence	“ in order to avoid dilution of a potentially contaminated harvest ….”	“If multiple harvests are performed for a single vaccine lot, testing may need to be performed on each individual harvest….For example, this may be relevant when the test method used has a low sensitivity”	-	Minor
III.E. 5. Post-Filtered Harvest or Final Bulk	§ 1	“These include testing for levels of residual cellular proteins and cellular nucleic acids.”	“These may include testing for levels of residual cellular proteins and cellular nucleic acids.”	Include the term “may” to allow flexibility in the need for routine testing as it may be possible to omit these tests from routine testing if the manufacturing process is validated to consistently achieve the specification. Additionally, this will align with WHO Guidelines to	Major

Section	Line/Paragraph	Current Wording	Suggested Change (revised wording)	Comment/Rationale/Reason for Change	Critical/ Major/ Minor/ Editorial
				assure the quality, safety and efficacy of live attenuated Rota virus (oral).	
IV. A. Testing of adventitious agents	§ 1	"Your biological starting materials should be characterized to ensure that they are free from extraneous infectious organisms such as bacteria, fungi, cultivatable and non-cultivatable mycoplasmas and spiroplasma, mycobacteria, viruses..."	"Your biological starting materials should be characterized, if appropriate, to ensure that they are free from extraneous infectious organisms such as bacteria, fungi, cultivable and non-cultivable mycoplasmas and spiroplasma, mycobacteria, viruses...In developing a characterization plan, consideration should be given to factors such as country of origin of the	Depending of the source (country, organ) of the raw materials, certain tests are not relevant.	Minor

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			materials, tissue type, etc.”		
IV. A. Testing of adventitious agents	§ 2	“For each of the suggested adventitious agent tests, alternatives such as those recommended by the WHO or the EP might be considered if justified with data showing sensitivity comparable to the recommended test.”	“For each of the suggested adventitious agent tests, use of alternatives such as those recommended by the WHO or the EP should be justified with appropriate data showing comparable sensitivity.”	Provides additional clarity/strength of argument to acknowledge that FDA will accept methods which have been accepted by other bodies, provided sufficient supporting data are available.	Major
IV. A.1. In vivo tests	1 §	“In the development of viral vaccines…and suckling mice inoculation of embryonated chicken eggs.”	“In the development of viral vaccines…and suckling mice.”	Remove the embryonated eggs for the testing of virus seed in order to align with Ph Eur. And WHO	Major
IV A. 1. e Embryonated Chicken Eggs	3 §	“ Both the initial pool and the passaged harvest should be tested for the presence of hemagglutinating agents with red cells from guinea pigs, humans (type O) and an avian species”	“ Both the initial pool and the passaged harvest should be tested for the presence of hemagglutinating agents with red cells e.g. from guinea pigs, the animal source being chosen based on the passage	The routine manipulation of human red blood cells is of increasing concern from a personnel safety perspective. The proposal is to keep only guinea pig red blood cells. A broader spectrum of relevant red blood cells should be used for extensive characterization	Major

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			history."	of Cell Banks and Seeds.	
IV. A. 1.f Antibody Production Tests	§ 2 first sentence	"A specific in vivo test for LCMV …when specific concerns about LCMV exist (ie. Antibody detected)…"	-	Not clear. If no Ab against LCMV detected, can we conclude that there is no concern, therefore no requirement?	Minor
IV. A.2.a.ii. Monkey kidney cells	§ 2	"The cell cultures should be observed for at least two weeks. After two weeks of observation, supernatants or lysates are subcultured onto fresh cells and observed for at least an additional two if appropriate…"	The cell cultures should be observed for at least two weeks. Based on the passage history and if a contamination is suspected, supernatants or lysates are subcultured onto fresh cells and observed for at least an additional two weeks if appropriate	It is unclear from the text to what stage of the manufacturing process the document is referring (ie. Cell culture or harvest). Assuming the document is referring to the harvest stage, the (14d + 14d) requirement specified differs from the revoked 21 CFR Part 630 Additional Standards and the requirement of the Ph. Eur,. and from the test described in the WHO TRS. The additional 14 days will have as significant impact on the turn-around time for testing and the capacity/throughput capabilities of most quality laboratories.	Major

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IV. A.2.a.ii. Monkey kidney cells	§ 4	"The test for haemadsorbing and hemagglutinating viruses is generally performed at the end of the observation period using guinea pigs, chicken and human type O RBCs."	"The test for hemadsorbing and hemagglutinating viruses is generally performed at the end of the observation period using guinea pigs RBCs."	In order to align with the Ph. Eur. Paragraph 2.6.16 that requires only guinea pigs RBCs.	Major
IV.A.2.a	Last paragraph			As this test can detect compromise by an adventitious virus during manufacturing, substituting the control cells for the production cells can yield meaningful data only if the control cells are handled in an identical manner as the production cells.	Minor
IV. A.2.c. Biochemical tests for retroviruses	§ 3	For example, products manufactured from primary cells might need to be assessed lot-by-lot.	For example, products manufactured from primary cells might need to be assessed lot-by-lot unless proven consistency has been demonstrated.	Provisions for demonstrated consistency should be added; as is the case for manufacture of flu vaccines.	Minor
IV.A.2.c IV.A.2.d			Suggest that these 2 sections be placed into a	Retroviruses are endogenous sequences in the production	Minor

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			separate section	substrate, rather than adventitious contaminants.	
IV.B. Testing of cell properties		-	-	There is no test description for identity test of cell substrate.	Minor
IV. B.2. Testing for oncogenicity	§ 1	"If your vaccine is manufactured in a cell substrate that was derived from a tumor or that has developed a tumorigenic phenotype through an unknown mechanism, it might carry a higher theorical risk of containing oncogenic substance."	"If your vaccine is manufactured in a cell substrate that was derived from a tumor or that has a tumorigenic phenotype through an unknown mechanism, it might carry a higher theorical risk of containing oncogenic substance."	The test should only be required for cell lines with tumorigenic potential or derived from tumors	Major
IV. B.1. Tests for tumorigenicity	§ 8	"Weakly tumorigenic cells might require between 4 and 7 months to form tumors in nude mice."	"Weakly tumorigenic cells might require up to 3 months to form tumors in nude mice."	Reduce to three months in order to align with Ph Eur and WHO for 84 days.	Major
IV.B.4	Third sentence	'..be expressed at equivalent levels ..'	'..be expressed at comparable levels ..'		Editorial
IV.B.4	Sixth sentence			Relevance of reference to Q2B (methods validation) is not clear	Minor
IV .C. 2. Testing for	§ 3	" For widely used human diploid cell	" For widely used human diploid cell	FRhL-2 cells are also well-characterized diploid cells.	Major

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residual DNA		strains, such as MRC-5 and WI-38, measurement of residual DNA might be unnecessary”	strains, such as MRC-5, WI-38 and FRhL-2 cells measurement of residual DNA might be unnecessary”	Add this cell lines to be consistent with paragraph on tumorigenicity	
IV .C. 2. Testing for residual DNA	§ 3	“You should limit residual DNA for continuous non-tumorigenic cells, such as low-passage Vero cells, to less than 10 ng/dose for parenteral inoculation as recommended by WHO.”	“You should limit residual DNA for continuous non-tumorigenic cells, such as low-passage Vero cells, to less than 10 ng/dose for parenteral inoculation and to less than100 µg/dose for oral vaccine as recommended by WHO.”	Reference should be made to the WHO “Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccine” for where the an acceptable limit of not more than 100µg of cellular DNA per human dose is likely to provide an adequate margin of safety for orally-delivered vaccines	Major
Glossary / p42	Item 22	-		Please include definition	Minor
Glossary / p42	Item 33 / second sentence	- ‘..demonstration of what characteristics the process is capable of performing ..’		Please clarify	Minor
VII Reference List	Ref. 6	- ICH Guideline Q2A		As of Nov, 2005, ICH Guideline Q2A was replaced by Q2(R1). A search for Q2A on both the CBER and ICH websites results in no Q2A	

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				document. However, FDA has not notified public of new Q2(R1) in Federal Register.	
Table 1	§ Virus seed	- Spiroplasma on virus seed - Identity, potency, infectious titer	- Spiroplasma if appropriate - Remove this testing	- Spiroplasma testing required if insect origin. - Tests done on harveststep final	Major
Table 1	§ Control cell cultures	- spiroplasma - *in vivo* adventitious agents - bovine and porcine viruses - BK - Specific agents	Remove these tests	Testing performed on viral harvest.	Major
Table 1	§ Master cell bank	- spiroplasma - tumorigenicity (except rodent cell lines)	- spiroplasma (if applicable) - tumorigenicity (except rodent cell lines and tumorigenic cell lines)	- Spiroplasma testing required if insect origin.	Minor
Table 1	§ Vaccine bulk	- spiroplasma - *in vivo* adventitious agents - RT assay	- Remove these testing at this step - RT assay (if applicable)	Testing done on seed and cell bank	Minor
Table 1	§ Final filled	Spiroplasma	Remove	Spiroplasma testing done on	Minor

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	product			seed and cell bank if applicable	