November 14, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-1999-D-0081: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the draft guidance titled "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up".

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO applauds the FDA on the work done to develop this Draft Guidance along with its companion documents on the topic of Gene Therapies. We find the Agency's Draft Guidance regarding product testing for replication competent retrovirus (RCR) to be well-reasoned and we concur with most recommendations. Particularly, BIO commends the Agency for inviting the Gene Therapy community to publish findings of relevant studies. BIO believes such an effort can potentially benefit and advance the field. In addition, FDA should consider conveying a public workshop with industry, academic experts, and other key stakeholders to discuss current scientific data regarding RCR in gene therapy applications that would be of tremendous benefit for all parties involved. BIO would be happy to work with the Agency on such effort. Lastly, there are a number of passages in the Draft Guidance that BIO believes would benefit from further clarity. We have provided more detailed information on the table below.

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance titled "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up". We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
III. RECOMMENDATIONS FOR PRODUCT TESTING		
A. Material Testing		
Lines 204-240	Non-homologous recombination to produce an RCR is a random event that can occur at an extremely low frequency (based upon accumulated data in the literature with current generation vector designs). The FDA should allow for a consideration that a vector manufactured in a well characterized producer cell line (or even in a transient transfection system) would have negligible risk of producing an RCR, and thus is a justification to discontinue RCR testing for transduced cells altogether on the basis of lot-to-lot testing of bulk vector. For instance, each vector lot can contain between 10^8-10^{10} vector particles (100 million to 10 billion). If the RCR detection assay can detect 1 RCR in a lot with 95% confidence, and the manufacturer produces 10 vector lots without an RCR detected, then the chances that an RCR would be generated by the vector production process is less than 1 in 100 billion. We thus believe the risk is negligible to warrant continued RCR testing of transduced cells.	Suggest that in Section III A.1.3 FDA consider including examples where routine RCR testing for vector may not be warranted for vector used in the manufacture of transduced cell products. For example, for vector manufactured with well characterized producer cell lines or even a platform transient transfection system.
Lines 254-258	The guidance states that "if you have accumulated manufacturing and clinical experience that demonstrates that your transduced cell product is consistently RCR-negative (section III A.1.3 of draft guidance), we recommend that you provide this data	Suggested addition at the end of line 258: "Separately, if the manufacturer can show in a controlled study using a model RCR that could be generated by the vector production process (with characteristics reasonably

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	to support reduction or elimination of testing ex vivo genetically modified cells for RCR." If RCR testing of the transduced cells is continued to be required (see also prior 2 comments in this section), it may be possible to conduct a controlled study in a transduced cell population using a model virus that, should a putative RCR be present, it would not be amplified, and thus support elimination of testing ex vivo genetically modified cells for RCR instead of accumulating manufacturing and clinical experience.	likely to represent a putative RCR) would not be amplified in the transduced cell population, it can be provided to support reduction or elimination of the testing of transduced cell product".
B. Amount for Testing		
Lines 288-301	It is possible that testing to a level of <1 RCR/dose may be less tractable for products intended for *in vivo* dosing.	BIO suggested addition at end of line 301: "If it is not feasible to test to a level of <1 RCR/dose equivalent, as may be the case with certain in vivo retroviral vector-based gene therapies in the early stages of development, sponsors should provide the rationale for the quantity of supernatant tested in the description of RCR testing procedures in your IND."
Line 301	eCTD Sections for Analytical Procedures listed as 3.2.S.4.2 and 3.2.P.4.2.	BIO suggested edit: "… in the eCTD section: Analytical Procedures ~~**3.2.S.4.2 or 3.2.P.4.2**~~ 3.2.P.5.2.
C. Assay for Testing		
Lines 323-326	Regarding RCR assays, the Agency should reconsider its recommendation of a fixed minimum number of passages (5) for amplification. Instead, the appropriate number of passages should be defined as that which ensures the recommended 95% probability of detecting 1 RCR/dose equivalent, as	BIO suggested change: "Vector supernatant assays should include culture of supernatant on a permissive cell line for as many passages as deemed necessary to ensure the proper assay sensitivity as described above in Section III.B.1. ~~a minimum of five passages in order~~

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	determined via method qualification and validation using a model virus with characteristics that would be expected to occur with the generation of a putative RCR in the vector system employed by the sponsor.	~~to amplify any potential RCR present.~~"
Lines 335-337	Testing each lot of vector supernatant for inhibitory effects on RCR detection seems redundant. Since the composition of the supernatant should not change significantly from lot to lot, the inhibitory effects on the assay should be consistent across lots for a given manufacturing process. Nevertheless, we do concur that the use of a positive control at an appropriate level and with appropriate replicates is key to ensuring assay sensitivity on a run-to-run basis.	BIO suggest the following sentence is deleted: "Each lot of retroviral vector supernatant should be tested for inhibitory effects on detection of RCR by using positive control samples that are added to vector supernatant."
Lines 347-360	The use of the RCR material described in this paragraph is consistent with that of a positive control, not a reference standard. We concur that the RCR material should be characterized as described in lines 357-358, but the use of the term "reference standard" suggests far more extensive characterization per ICH Guideline Q6B.	BIO suggests "reference standard" is changed to "positive control" where appropriate.
IV. RECOMMENDATIONS FOR PATIENT TESTING		
A. RCR Testing Schedule		
Lines 370-377	Given the FDA's recommendation in Lines 388-390 regarding testing of samples following an "adverse event suggestive of a retrovirus-associated disease," we believe that active monitoring of patient samples following administration of the transduced cell product for the purposes of detection of RCR is unwarranted. This would presume that an RCR is	Suggest the FDA eliminate RCR testing of patient samples and instead allow Sponsors to archive all patient samples without testing and only allow testing if clinical manifestations warrant it.

SECTION	ISSUE	PROPOSED CHANGE
	either generated post transduction or otherwise exists that was not detected in the vector lot. Given the accumulated experience in the field over the past 20 years (i.e., lack of evidence to demonstrate that such an event would occur, or if it did, would do so with an extremely low probability), we believe such testing should be eliminated. An alternative is to archive all patient samples without testing and only do so if clinical manifestations warrant it (i.e., that an emergent adverse event is suggestive of a retroviral-associated disease).	
Lines 372-377	More clarity is needed regarding what actions should be taken in case a post-treatment sample is found to be a confirmed positive for RCR. As well as to when can testing be discontinued following the requested "further analysis".	BIO suggest the FDA provide further clarity on the actions to be taken when a post-treatment sample is found positive for RCR. In addition, BIO suggests the following change: "pre-treatment, followed by testing at three, six, and twelve months after treatment, ~~and yearly for up to fifteen (15) years.~~" As this language will not routinely apply.
Lines 372-376	It is unclear what the distinction between the planned analysis of patient samples (lines 372-374) and the collection and storage of patient samples (alluded to in lines 375-376).	FDA should provide clarity on these terms.
Lines 387-388	It is unclear if the term "other hematologic disorders" is referring to non-malignant conditions (i.e., in contrast to "cancer" mentioned in line 387).	BIO suggest clarifying this passage if specific nonmalignant hematologic disorders should be included among the clinical outcomes to be assessed. Otherwise, BIO suggests striking the word "other" in line 388.
B. Recommended Assays		
V. DOCUMENTATION OF RCR TESTING RESULTS		

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VI. POST-LICENSURE CONSIDERATIONS		
Lines 439-441	More clarity is needed to understand the intended scope of the request to assay for RCR. It is unclear what causes of death or what time period post-administration should be subject to RCR testing of patient tissue. We believe that RCR testing should only be warranted in the event that an emergent adverse event is suggestive of a retroviral-associated disease.	BIO suggest the following edit: "In the event patients die of a suspected retrovirus-associated disease or develop neoplasms within 15 years following product administration, every effort should be made to assay for RCR in a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue."
Lines 443-444	It is unclear whether patient follow-up should take place for up to 15 years post-dosing or post-licensure. We presume the Agency intends the former to be their recommendation.	BIO suggest the following edit: "After licensure of retroviral-based gene therapy products, we also recommend continued long term patient follow-up for up to fifteen (15) years after dosing, ~~after licensure of retroviral-based gene therapy products~~ to monitor for delayed adverse events."