Biotechnology Industry Organization

November 19, 2014

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

Re: Docket No. FDA-2014-D-0852: Draft Guidance for Industry on Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products." BIO greatly appreciates the Agency's work to develop this guidance and notes our support expressed previously in comments on the *Draft Guidance for Industry on Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*.[1]

BIO represents more than 1,000 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO thanks FDA for developing this Draft Guidance document to inform the gene therapy community that it will require shedding data from clinical studies and that this information might be included in the package insert for licensed products. Since FDA typically will not request that shedding studies be conducted during Phase 1, this requirement may not be raised with a Sponsor until later in product development, after safety has been demonstrated and a potential for efficacy has been determined. Given the complexity of the shedding studies and the need to design assays that will yield reliable data across different sample matrices, BIO believes that Sponsors will need to

[1] BIO Comments to FDA on *Considerations for the Design of Early-Phase Clinical Trials for Cellular and Gene Therapy Products* (2014), available at http://www.bio.org/advocacy/letters/bio-submits-comments-considerations-design-early-phase-clinical-trials-cell-and-gen

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begin planning and budgeting for these studies early in development. As such, we recommend early communications regarding potential shedding studies between the Agency and the Sponsor.

The data generated from clinical, and perhaps preclinical, shedding studies will be used to develop risk mitigation and communication strategies for patients who receive oncolytic and/or virus or bacteria-based gene therapy (VBGT) products, as well as their close contacts, their treating physicians, and the general public. As such, it is of utmost importance that the data generated from shedding studies be based on sound scientific principles to ensure confidence in the risk mitigation and communication strategies that are derived from them.

Use of Terms and Definitions

BIO recommends that the terms "product" and "product-based viruses and bacteria" be defined and used consistently throughout the document. In Section I, shedding is defined as the release of oncolytic or VBGT "products" from the patient through excreta, secreta, or skin. Furthermore, shedding is stated to raise the "possibility of transmission of 'product-based' viruses and bacteria from treated to untreated individuals". BIO believes that it is unclear if a distinction is being made between portions of oncolytic and VBGT products (*e.g.* DNA fragments, capsid and/or other viral proteins) and intact, infectious oncolytic and VBGT products, and if shedding is considered to encompass the release of both portions, as well as infectious oncolytic and VBGT products. As we note in our specific comments below, for the purpose of shedding and transmission risks, the term "product" should be limited to the intact viral or bacterial therapeutic.

Furthermore, as a change to the transgene carried by recombinant oncolytic or VBGT products is unlikely to have an impact on the potential for replication, shedding, or transmissibility, we believe the Draft Guidance should include discussion of the possibility of using existing preclinical and clinical shedding data obtained from studies of products belonging to the same "class" to support transmissibility risk assessments if the products are administered at similar dosages and routes.

Utility of Preclinical Shedding Studies

BIO finds the Draft Guidance to contain conflicting information about the utility of preclinical shedding studies. For example, in Section IV, the inadequacy of preclinical shedding data for the purpose of predicting the shedding profile in humans is given as justification for the need to conduct shedding studies during clinical development. However, in Section VI, shedding data from animal studies is considered to be useful for estimating the likelihood and potential shedding profile in humans. Further, it is stated in Section VII that for replication incompetent vectors, shedding analysis is only required later in development once a dose has been selected. We note that if this is the case, it is unclear if there would be any need for preclinical shedding analysis. FDA should clarify whether preclinical shedding studies are required and the role that the data

derived from these studies can play in the design of the clinical shedding study, including the potential to preclude the need for clinical shedding studies in the event that no evidence of VBGT product shedding is found. For example, BIO believes that additional guidance on this topic in Section VI would be useful (*i.e.,* Preclinical shedding studies are recommended for replication competent vectors).

Clinical Shedding Studies

BIO requests that additional guidance be provided on the design of clinical shedding studies to ensure that the data and subsequent risk assessments for different products are based on sound scientific principles and study design. Issues for which further guidance is needed include:

- Number of subjects to include in shedding study: Considering the diverse development pathways for VBGTs based on indication, the overall number of subjects exposed to the product at the time of licensure will vary dramatically. For example, products with rare disease indications in which development may be compressed into a Phase 1/2 study, followed by a single pivotal study, may have overall exposures of fewer than 50 subjects, while products in development for cardiac or cancer indications may include over 100 subjects in a single Phase 2 study. In addition, we recommend that considerations on how overall exposure to the product during clinical development might affect the timing and number of shedding studies conducted be discussed.

- Assay sensitivity and specificity: Several assay methods are discussed in the Draft Guidance, but standards for sensitivity (minimal limit of detection) are not provided. Furthermore, recommendations are given to extend shedding analysis beyond quantitative polymerase chain reaction (qPCR) if shedding is "significantly above the limit of detection (LOD)" is detected. BIO recommends that the Guidance further define the level of detection above the LOD that would necessitate additional studies to characterize the infectivity of the detected product-related nucleic acid. Additionally, we request that the Guidance include a recommendation to collect baseline samples prior to treatment as a negative control.

- Sample analysis-timing: The Draft Guidance suggests that shedding analysis might be an iterative process, with decisions about both the appropriate analysis to be conducted and the number of sampling time points dictated by the results obtained. However, BIO notes that a clinical study may include multiple clinical sites and testing may occur at a centralized laboratory, meaning samples will likely be batched for processing and testing. Multiple patient samples from multiple time points will therefore likely be assayed at once, meaning that the duration of sample collection should be prospectively planned. Similarly, if qPCR of samples is to be followed by infectivity assay, portions of the sample will need to be reserved and should be considered during sample collection.

- Infectivity determination: Sponsors may choose to conduct a series of studies aimed at determining if shed material is likely to be infectious, including conducting infectivity assays that directly demonstrate whether shed material is infectious, or they may choose to conduct a simple qPCR assay for small genome fragments. If the latter approach is taken, the Agency will assume that the shed material is infectious. BIO finds it unclear how patients, treating physicians and the public at large will be able to assess the risks related to these products when the underlying body of evidence supporting conclusions about infectivity and, therefore, transmissibility are so variable. BIO recommends that the Agency consider whether more standardized approaches can be developed to assess the risks associated with oncolytic and VBGT products, perhaps based on what is known about the biology of the parent viruses and bacteria, the modifications made to the vectors, and information collected over the past 20 years of clinical research with these vectors.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
	The Draft Guidance states "For purposes of this guidance, the term "shedding" means release of oncolytic or VBGT products from the patient through one or all of the following ways: excreta (feces); secreta (urine, saliva, nasopharyngeal fluids etc.); or through the skin (pustules, sores, wounds)."	While blood is not considered a shedding route, BIO believes that data must be collected as part of pharmacokinetic analysis to understand the extent of product dissemination from the site of administration and the kinetics of product clearance.
	The Draft Guidance states "Shedding raises the possibility of transmission of product-based viruses and bacteria from treated to untreated individuals."	BIO recommends defining "untreated individuals" (close contacts and clinical/medical staff).
II. SCOPE		
III. BACKGROUND		
IV. WHY COLLECT SHEDDING DATA DURING CLINICAL DEVELOMENT?		
Paragraph 1	The Draft Guidance states "Shedding studies of oncoloytic or VBGT products are conducted to provide information about the likelihood of transmission to untreated individuals and about measures to prevent such transmission."	BIO suggests re-phrasing this statement to emphasize that measures to prevent transmission require some initial knowledge of shedding: "Shedding studies of oncoloytic or VBGT products are conducted to provide information about the likelihood of transmission to untreated individuals, ~~and about~~ which can

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		be subsequently used to evaluate measures to prevent such transmission."
Paragraph 1	The Draft Guidance discusses the rationale for conducting shedding studies.	BIO requests that the Agency clarify that, where feasible with viral therapies, the administration of anti-viral therapy should be considered to evaluate the effectiveness to reduce or shorten the duration of shedding or the incidence of re-activation after the viral therapy is discontinued.
Paragraph 1	The Draft Guidance states "Shedding data collected during clinical development should provide a clear and comprehensive understanding of the shedding profile of oncolytic or VBGT products in the target patient population(s)."	BIO notes that the extent of shedding could vary if the route of administration or dosing frequency is changed during development. As such, we recommend rewording to: "Shedding data collected during clinical development should provide a clear and comprehensive understanding of the shedding profile of oncolytic or VBGT products in the target patient population~~(s)~~ and route of administration."
V. DESIGN OF SHEDDING STUDIES: GUIDING PRINCPLES		
Paragraph 1	The Draft Guidance states "The main considerations in the design of shedding studies are: the choice of clinical samples that are collected from subjects in a trial (feces, urine, nasal swabs etc.); the periodicity of sample collection and duration of the monitoring period; and the assay methodology selected to test for the presence of the shed oncolytic or VBGT product in the clinical sample (Ref. 1)."	BIO believes that the main considerations should include analysis of impact of immunogenicity on shedding. As such, we recommend rewording to: "The Main Considerations in the design of shedding studies are: the choice of clinical samples that are collected from subjects in a trial (feces, urine, nasal swabs etc.); the periodicity of sample collection and duration of the monitoring period; ~~and~~ the assay methodology selected to

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		test for the presence of the shed oncolytic or VBGT product in the clinical sample (Ref. 1); and the effect of immune response to the product on the extent and duration of shedding."
A. BIOLOGICAL CHARACTERISTICS		
Immunogenicity	BIO believes that the Draft Guidance is unclear as to when it would not be sufficient to descriptively analyze the time-course of shedding for multiply administered products.	BIO believes it would be informative to provide an example where it would be necessary to more definitively evaluate a shedding time-course.
Persistence and latency	BIO believes that the Draft Guidance is unclear when surveillance is appropriate, what aspects should be considered to define the appropriate duration of follow-up and sample size to detect reactivation to avoid perpetual data collection.	BIO believes it would be informative to provide examples of appropriate follow-up and sample size for specific circumstances, and the criteria for assessing when data is conclusive so that surveillance can end.
Persistence and latency	BIO believes that the Draft Guidance is unclear if a product's exhibition of persistence of latency capability or parent virus/bacteria of the product should be considered.	BIO requests that the Agency clarify that a product's exhibition of persistence of latency capability or parent virus/bacteria of the product should be considered.
B. ROUTE OF ADMINISTRATION		
	The Draft Guidance states "For example, to assess shedding in patients administered an oncolytic virus by the intradermal route…"	BIO believes that additional guidance should be provided on acceptability of intradermal route as a surrogate for intra-tumoral route or if the preference is for data from intra-tumoral route with the resulting amplification of dose in

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		conditionally replicating oncolytic products. We recommend rewording to: "For example, to assess shedding in patients administered an oncolytic virus by the intradermal or intra-tumoral route,…"
	The Draft Guidance states "Similarly, we recommend the collection of nasopharyngeal washes when an oncolytic virus is administered by inhalation or via the intranasal route."	BIO finds it unclear whether these sample types also should be collected if dosing is by direct injection but in related tissue (lung / head and neck)? We recommend rewording to: "Similarly, we recommend the collection of nasopharyngeal washes when an oncolytic virus is administered by inhalation or via the intranasal route or if this is warranted if the target site of administration is local to tissue exposed to these route of administration."
VI. COLLECTION OF SHEDDING DATA IN PRECLINICAL STUDIES		
	The Draft Guidance refers to the "product" without any specifics or clarification on what is meant. BIO notes that the transgene is unlikely to have an impact on the potential for replication and shedding, thus, this section should specify that the product is intended to mean the viral vector portion of the overall product.	BIO requests that the Agency clarify when referring to "the product" that they are referring to the intact oncolytic or VGBT therapeutic.

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Paragraph 1	The Draft Guidance discusses that preclinical shedding studies may be useful and can help estimate the likelihood and potential shedding profile in humans.	BIO recommends that FDA clarify that shedding studies conducted in nonclinical species should be conducted in relevant animal models (*e.g.,* demonstrating similar infectivity patterns as in humans), as the use of irrelevant animal models is misleading and uninformative.
Bulleted List	BIO notes that an important rationale for nonclinical testing is the unique route of administration.	BIO recommends adding the following new bullet: "Proposed clinical administration route of the oncolytic or VBGT differs from the natural route of exposure/infection."
Paragraph 2	The Draft Guidance states "The use of the animal species/model(s) is an important factor that can affect the biological relevancy of the shedding profile generated in the animal."	BIO believes that interpretation of pre-clinical shedding and distribution data may be impacted by pre-existing immunity. As such, we recommend rewording to: "The use of the animal species /model(s) ~~is~~ ~~an~~ are important factors that can affect the biological relevancy of the shedding profile generated in the animal. Because immunogenicity can affect clearance, consideration of shedding in animals should be interpreted in the light of any pre-existing anti-drug antibodies."
Paragraph 2	The Draft Guidance discusses considerations for the use of animal species/model(s).	BIO recommends including guidance on the route of administration in preclinical studies. As such, we suggest adding the following text to the paragraph:

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		"…preexisting immunity the animal has to the product. Shedding studies conducted in animal models should mimic the intended clinical administration route to the extent possible."
VII. COLLECTION OF SHEDDING DATA IN CLINICAL STUDIES		
A. WHEN TO COLLECT SHEDDING DATA IN CLINICAL STUDIES		
	The Draft Guidance states "For products classified as replication competent, we recommend that Sponsors begin collecting shedding data in Phase 1 trials." BIO believes that the Guidance should specify that shedding is collected from first dosing in first in human (FIH) studies not just during Phase 1 trials.	BIO recommends rewording to: "For products classified as replication competent, we recommend that Sponsors begin collecting shedding data ~~in~~ from the start of FIH/Phase 1 trials or on changes to a new route of administration."
B. STUDY DESIGN		
Paragraph 1	The Draft Guidance states "The plan to collect shedding data in clinical studies can be based on prior clinical experience with the same or similar product…" BIO believes that the design of the collection plan could also be based on experience with the wild type parent virus/bacteria.	BIO recommends rewording to: "The plan to collect shedding data in clinical studies can be based on prior clinical experience with the same or similar product or parent virus/bacteria…"

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Duration of sample collection; bullet 2	The Draft Guidance states "When treated with replication competent oncolytic or VBGT products, immunosuppressed patients may become persistently infected and may shed the product for extended periods of time (Ref. 2)."	BIO requests that the Agency clarify the following points: • For products with a cancer indication, is there a standard requirement for expanding the schedule for collection of shedding data for persons who are immunosuppressed? • How is *immunosuppressed* defined?
Duration of sample collection; bullet 4	The Draft Guidance states "If an oncolytic product is based on a herpes virus that has the potential for latency reactivation, we recommend the collection of additional samples for shedding analysis when clinical signs warrant…"	BIO recommends adding the scope of potential sources of reactivation. As such, we request that FDA revise to read: "If an oncolytic product is based on a herpes virus that has the potential for latency reactivation, we recommend the collection of additional samples for shedding analysis when clinical signs of either the wild type parent or any potential product reactivation warrant…"
Type(s) of sample	The Draft Guidance states "The natural route of transmission and shedding of the parent virus or bacterium from which the product is derived from also is considered in the choice of clinical samples." BIO notes that the parent herpes virus may be shed from genital mucosa, although it is not an expected route of transmission of the product virus.	BIO requests that the Agency clarify that where the parent organism's natural route of shedding may be different from the expected product virus, sampling of the additional tissues (*i.e.,* genital mucosa) is required.
VIII. ANALYTICAL ASSAYS TO MEASURE SHEDDING		

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Bullet 1	BIO notes that viral load as measured by qPCR is not indicative of infectious virus and should be interpreted with caution. References that discuss the discordance between qPCR and infectivity: 1. Schiffer, J. T., et al. (2011). "Detailed analysis of mucosal herpes simplex virus-2 replication kinetics with and without antiviral therapy." J Antimicrob Chemother 66(11): 2593-2600. 2. Schiffer, J. T., et al. (2011). "The kinetics of mucosal herpes simplex virus-2 infection in humans: evidence for rapid viral-host interactions." J Infect Dis 204(4): 554-561.	BIO recommends adding the following text to the end of the first bullet: "However, detection of viral fragments by qPCR does not indicate intact virus or inform infectious potential."
	The Draft Guidance discusses the use of assays. We believe that at a minimum, the assay should discriminate the therapeutic from prior wild-type infection. Detection of mutation/recombination should be considered.	BIO recommends adding the following text to the end of either the first or last bullet: "The qPCR assay should be designed to discriminate between background/wild-type infections."
Bullet 2	The Draft Guidance states "For replication competent products, detection of nucleic acids should be followed up with infectivity or growth-based assays."	BIO recommends that FDA revise to read: "For replication competent products, detection of nucleic acids should be followed up with infectivity or growth-based

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	BIO believes that Sponsors should have the option of justifying the use growth based assays first (at injection site etc. where product will be present but may not be live).	assays. Detection of nucleic acids would be followed up with infectivity or growth based assays if these were not used in the initial screening. Replication competent products…"
Bullet 3	The Draft Guidance states "If shedding is noted by qPCR assay at a level significantly above the limit of detection (LOD), we recommend that Sponsors further characterize the shed material for infectivity or growth to confirm the absence of any potential replication-competent variants of the product that may have emerged." BIO believes that the term "significantly" is too vague.	BIO requests, considering the impact of developing an infectivity assay for such a purpose, that FDA indicate what is meant by "significant" (*e.g.*, 100-, 1000-, 10,000-fold, etc., above the LOD).
IX. ANALYSIS OF SHEDDING DATA		
A. THE NATURE OF SHED MATERIAL		
B. THE EXTENT OF SHEDDING		
X. WHAT TO INCLUDE IN A CLINICAL SHEDDING STUDY REPORT		
	The Draft Guidance suggests providing a shedding report as the information is obtained during product development, and	BIO recommends that FDA provide additional guidance on timing of the initial shedding report.

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	a full report should be provided in the BLA.	
XI. ASSESSING THE POTENTIAL FOR TRANSMISSION TO UNTREATED INDIVIDUALS DUE TO SHEDDING		
A. WHAT INFORMATION IN THE SHEDDING DATA CAN BE USED TO ASSESS POTENTIAL FOR TRANSMISSION TO UNTREATED INDIVIDUALS?		
B. MONITORING UNTREATED INDIVIDUALS FOR TRANSMISSION		
	The Draft Guidance states "Because transmission to untreated individuals is an extremely low probability event, monitoring such individuals for transmission is usually not required during the clinical development of a product."	BIO recommends that FDA add examples of untreated individuals and potential scenarios of transmission along with reporting frequencies. Although we note that secondary transmission to untreated individuals to healthcare providers and close contacts is an extremely low probability. BIO recommends that FDA provide additional advice on monitoring clinical staff (for example needle sticks): "Secondary transmission to untreated individuals. Clinical signs and symptoms of infection due to secondary transmission to untreated individuals, and data from any accidental exposure of health care professionals (such as needle sticks) and follow up must be collected and reported periodically."
XII. REFERENCES		