Adenoviral Reference Material Working Group
Bid Submission Form
Vialing and Freezing Donation
RFP 6.0

Item for Submission

Vialing of an Adenovirus 5 Wild-type reference material bulk provided in final formulation. Bulk should provide enough material to fill at 0.5 mL in 4500 to 5000 vials at 2 to 5 x 10^{11} particles/mL. Vials are intended to be stored at ≤-55?C until shipped under proper conditions to institution(s) responsible as repository. Bidder will include sterility test of vials as part of bid.

General Requirements for Bidding

Finishing activities must be done under documentation equivalent to CGMP. Institution will need to provide evidence of their experience in finishing purified adenovirus or other similar biologicals and detail their facility and its capabilities. The facility description should address procedures to ensure segregation during filling of the reference material.

The purified formulated adenovirus reference material will be supplied from other bid activities in this process along with minimum handling instructions.. Indicate your minimum requirements or concerns for acceptance of this material if not addressed by characterization called for in RFP 5.0. The bid should indicate the amount of time required from receipt of the purified, formulated bulk reference material until completion of vialing, freezing, and sterility test of final containers.

The bidder should arrange sterility testing of the vialed reference material.

The proposal should include details of the proposed method/container for shipping to ensure integrity of the vialed reference material upon arrival at the repository facility.

Documentation Requirements

Documentation should include detailed information on the proposed container/closure system(s). Information should also be provided on the maximum number of vials that can be filled at one time; the amount of time for filling the proposed number of vials; handling and storing of bulk before and during fill. The proposal should address the following issues:

?? Container/closure system's ability to provide stability for storage of adenovirus at ≤-55°C
?? If filling is to be staged in specific numbers of vials, information regarding the institution's limitations and how the institution proposes to address these limitations

?? If documentation and practices equivalent to CGMP are not utilized, what other type of data can be provided to support fill (e.g., media fill using the proposed container/closure)
?? Environmental monitoring program

It is expected that the Batch Records used for the filling procedure and the environmental monitoring data collected will be made available.

The proposal should contain the proposed method for sterility testing of the vialed reference material.

Proposed details related to shipping of adenovirus reference material vials to repository(ies).

Please complete the following fields:

Contact Information – RFP 6.0

Contact Individual:	Joe Senesac
Institution:	Introgen Therapeutics, Inc.
Address:	2250 Holcombe Blvd. Houston, Texas 77030
Phone Number:	(713) 610-4020
Email Address:	j.senesac@introgen.com

Vialing and Freezing Donation Information – RFP 6.0

Please indicate if your institution is also submitting proposals for the other activities:

☐ Donation of Cell Bank

☐ Donation of Ad5 Wild-type Virus

☒ Ad5 Wild-type Virus Bank Production

☒ Ad5 Wild-type Purified, Formulated Bulk Production

☐ Donation of Repository Services

☐ Donation of Supplies/Other Services

Please attach: Procedure for Vialing
Proposed Container/Closure Information
Institution Capability Statement
Media Fill or Other Validation Information as available
Information on shipping

Submit this completed form and all attached information for receipt **by February 28, 2001** to the address below. Electronic submissions are encouraged. Final decisions will be communicated by or about March 31, 2001. Please note that all information submitted will be publicly available. Please do not mark any information confidential, as we cannot honor that request. Please estimate the cost and market value of donated goods and services.

Williamsburg BioProcessing Foundation
Attn: Adenovirus Reference Material Working Group
4015 Killam Avenue
Norfolk, VA 23508

PH: 757-423-8823
FAX: 757-423-2065

EMAIL: advector@wilbio.com

A. Capability Statement

Introgen Therapeutics, Inc. (Company) is engaged in the manufacture, research and clinical development of viral vector-based gene therapies for cancer treatment. The Company utilizes a 12,000 square foot manufacturing facility at 2252 Holcombe Boulevard in Houston, TX for the production of viral vectors for non-clinical and clinical studies. This facility is fully commissioned and has been qualified via the production of three lots of an adenoviral vector, RPR/INGN 201, containing a functional copy of the human *p53* gene Ad5CMV-*p53*.

Introgen has produced over 30 clinical batches of various materials for Phase I to Phase III clinical studies. The facilities include class 100,000 down to Class 1,000 cleanrooms which provide two separate manufacturing suites and appropriate environments for Cell/Viral Culture, Purification, and Finishing activities. Key members of the manufacturing team have worked together at Introgen for greater than 5 years. Introgen also has fully staffed Quality Assurance and Quality Control departments for testing and oversight of production.

B. Production Requirements

Material to be filled, accompanied by a completed Certificate of Analysis as defined in RFP 5.0. It is preferred that the material be provided in three aliquots if larger bulks are provided.

C. Finishing and Freezing

Manual finishing operations will take place in a class 10,000 cleanroom equipped with a class 100 biosafety cabinet (BSC). All equipment and HEPA filters are in a current state of calibration or certification. The production will take place on a strict campaign basis, with the rooms thoroughly cleaned and disinfected prior to and at the end of production. Production personnel will be limited to working with a single construct each working day.

Product will be thawed at room temperature and sterile filtered into a sterile single use container before being held at refrigerated temperature overnight. The material will be held at room temperature during each fill. The fill line and fill needle are also sterile single use disposable. A programmable pump is used to accurately dispense the desired 0.5 mL fill volume. Crimping is performed with a West Capper crimper. A pilot study has been performed to demonstrate that an acceptable level of fill accuracy and consistency can be achieved.

Product will be filled in 3-4 fill runs (maximum 1500 vials per run), on separate days. A triplicate manual fill qualification of the appropriate size has been completed in a different room of the same class in this facility. A single fill qualification run of approximately 1500 vials will be executed in the room this product will be filled in. Standard environmental monitoring will be performed

for this operation, comparable to that done for Introgen fills of clinical-grade material.

The vials will be labeled using Introgen printed labels with a format agreed upon by the Adenoviral Reference Material Working Group. The label will contain the construct name, date of manufacture, a lot number and manufacturer. The label will not contain any concentration information, as that will be determined post-production.

D. Production Schedule

The filling schedule will be set when the delivery date is known. The fill operation will require approximately 5-10 working days. Sterility testing will require two weeks for completion. Complete release testing will require approximately six weeks.

E. Container Closure and Shipment

The glass vials used are contract supplied to Introgen Therapeutics, Inc. as sterile stoppered vials. The stoppered vials are aseptically packaged in stainless steel racks that are individually triple wrapped for cleanroom use. We have completed stability studies of up to 18 months in this container closure system.

Container closure details are as follows:

Vial - 3mL, 13MM Serum/Lyophilization Vial, Flint glass

Stopper – 13MM Grey Butyl Stopper

Crimp- Flip-off Button Crimp

Shipment of the vialed product will be on dry ice with the addition of a calibrated temperature trace device to document shipping conditions. The shipping container will be an EnduroTherm® insulated container.

F. Certificate of Analysis and Specifications

See attached proposed Certificate of Analysis containing specifications for testing to be performed on each sub lot.

G. Documentation

A detailed production report will be submitted upon completion of testing. The report will document the production methods, environmental monitoring results, and will include the completed Certificate of Analysis. This will be made available in lieu of completed production batch records.

Introgen Therapeutics, Inc.
Certificate of Analysis for Adenovirus Serotype 5 Reference Material
Lot #

Manufactured By: Introgen Therapeutics, Inc.
Adenovirus Vector Serotype 5 Reference Material
Virus Bank:
Cell Bank:

Lot Number
Date of Manufacture:
Number of Containers:
Store at -60°C or below

Test	Sponsor	Specification	Result
Sterility USP & EP	MDS Panlabs	Sterile	
Bacterial Endotoxins Test	Introgen	Report Value	
Titration of Adenovirus Vector	Introgen	Report Value	
Virus Particle Enumeration by A_{260}	Introgen	2E11 – 5E11 vp/mL	
A_{260}/A_{280} Ratio	Introgen	Report Value	
Purity by HPLC Ion Exchange	Introgen	Report Value	
Bovine Serum Albumin (ELISA)	Introgen	Report Value	
huDNA	TBD*	Report Value	
pH	Introgen	Report Value	

I certify that the above information has been accurately transcribed.

By: _____ _____
Quality Assurance Representative Date

* Testing will be performed at a CGMP facility but Introgen has not yet determined which test site will be used.