Request for Proposal

Ekobi® Embolization Microspheres

Proprietary and Confidential

Reply to:
Irwin Griffith
Chief Operation Officer

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INTRODUCTION AND BACKGROUND

IMBiotechnologies Ltd. (IMB) was established in 2008 for the purpose of commercializing embolotherapeutic medical devices. Corporate headquarters are located in Edmonton, Alberta, Canada.

PURPOSE OF THE REQUEST FOR PROPOSAL

Embolotherapeutic agents are designed to be delivered through an angiocatheter into the arterial blood supply feeding a tumor or target tissue. The embolic agent occludes the blood vessel, causing the blood to pool and form a clot. This significantly decreases the blood supply to the target tissue leading to tissue regression. Most commercially available embolic agents are permanent implants.

IMB's lead product is Ekobi® Embolization Microspheres (Ekobi). Ekobi microspheres are biodegradable and comprised of poly(lactic-c-glycolic acid) (PLGA) microspheres conjugated with bovine Type I collagen. Ekobi microspheres are hyperechoic and detectable using standard B-mode ultrasound. Ekobi Embolization Microspheres is regulated as a Class II device in the USA, a Class III device in Europe and a Class IV device in Canada.

IMB is seeking to identify and select an outside independent organization to manufacture Ekobi for commercial sales. IMB has received FDA 510(k) clearance and a Medical Device License from Health Canada for the Ekobi product. The product family includes seven products that differ in microsphere size but have the same bulk composition and intended use (Table 1). This Request for Proposal (RFP) focuses specifically on the manufacture of 5 of these family members for commercialization with intent to manufacture the remaining 2 members, Ekobi 501 and Ekobi 507, at a later date.

The remainder of this document provides additional information that will allow a contract manufacturing organization to understand the scope of the effort and develop a proposal in the format desired by IMB.

Table 1. Ekobi Family of Embolic Microspheres

Product	50 - 100 µm	**75 – 150 µm**	**150 - 180 µm**	**180-212 µm**	**212-300 µm**	**300-425 µm**	500-800 µm
Ekobi 501	✓						
Ekobi 502		✓					
Ekobi 503P			✓				
Ekobi 503L				✓			
Ekobi 504					✓		
Ekobi 505						✓	
OCL 507							✓

Bold products are the focus of this RFP

GUIDELINES FOR PROPOSAL PREPARATION

Award of the contract resulting from this RFP will be based upon the most responsive Contract Manufacturing Organization (CMO) whose offer will be the most advantageous to IMB in terms of cost, functionality, and other factors as specified elsewhere in this RFP.

IMB reserves the right to:

- Reject any or all offers and discontinue this RFP process without obligation or liability to any potential CMO,
- Accept other than the lowest priced offer,
- Award a contract on the basis of initial offers received, without discussions or requests for best and final offers, and
- Award more than one contract.

CMO's proposal shall be submitted in several parts as set forth below. The CMO will confine its submission to those matters sufficient to define its proposal and to provide an adequate basis for IMB's evaluation of the CMO's proposal.

In order to address the needs of this procurement, IMB is interested in working with a single CMO to manufacture Ekobi® Embolization Microspheres, with the right and need to procure a second manufacturing site as backup. IMB recognizes that the successful CMO may have to sub-contract certain portions of the work. IMB will recognize the integrity and validity of CMO team arrangements provided that:

- The arrangements are identified and relationships are fully disclosed, and
- A primary CMO is designated that will be fully responsible for all contract performance.

CMO's proposal in response to this RFP will be incorporated into the final agreement between IMB and the selected CMO(s). The submitted proposals are suggested to include each of the following sections:

1. Corporate Information, Overview and Executive Summary
2. Manufacturing
3. Regulatory
4. Project Management and Reporting
5. Cost Estimates
6. References

Appendices I – VI contain detailed questionnaires to be filled out for each of the requested sections. The supplied information will be important for evaluation of the respondent's proposal. Appendix VII describes the evaluation and selection process.

PRODUCT AND TECHNICAL INFORMATION

PRODUCT DESCRIPTION

Name:	Ekobi® Embolization Microspheres
Composition:	PLGA microspheres conjugated with collagen
Polymer:	75:25 poly(D/L lactic-co-glycolic acid)
PLGA source:	Supplied by IMB
Collagen:	Bovine type I
Collagen source:	Becton Dickinson – Avitene Microfibrillar Collagen Hemostat
Vial:	20 mL glass vial, borosilicate
Fill:	200 mg or 500 mg dry powder
Closure:	Teflon stopper
Seal:	Aluminum crimp seals, with tear-out tab
Stability:	48 months at RT

MANUFACTURING PROCESS

Description of the manufacturing process:

1. **Pellet Sieving**:

   PLGA pellets are supplied as a bulk raw material with a size range of approximately 75 µm to 500 µm. Wet sieving is necessary to remove any small polymer particles and any overly large polymer particles prior to the spheronization step. Sieving is accomplished using ASTM-qualified sieves that bracket the size range of microspheres to be produced. For this RFP, the sieving brackets are 75 µm to 500 µm to facilitate production of microspheres that fit within the Ekobi 502, Ekobi 503P, Ekobi 503L, Ekobi 504, and Ekobi 505 size ranges, as presented in Table 1.

2. **Spheronization:**

   Pellets from the pellet sieving step are spheronized by stirring in a liquid bath. Spheronization takes between 5 hours (minimum) and 8 hours. The microspheres produced from this step must be greater than 99% spherical as confirmed by visual inspection. Once the desired percentage spheronicity has been reached, heating of the reaction vessel is stopped. The microspheres produced can be left stirring in the reaction vessel, at room temperature, overnight prior to moving to the next step. The microspheres are washed with water for injection (WFI, or equivalent) after spheronization. *Details regarding spheronization will be provided as part of technology transfer.*

3. **Conjugation:**

   Washed microspheres produced from the previous step are treated, washed with WFI (or equivalent) and resuspended in buffer. A collagen suspension is added to the microsphere suspension and the collagen is cross-linked to the microspheres during an incubation step. Conjugation takes less than one hour. *Details regarding collagen preparation, specific reactant concentrations, and incubation times will be provided as part of technology transfer.*

   Conjugated microspheres are washed with PBS to remove unbound collagen.

4. **Size Separation:** Microspheres are wet-sieved according to the product size specifications using sieve stacks. Sieving is conducted manually.

   Microspheres separated into their appropriate size ranges are air-dried on the respective low-end size sieve.

   Particle size analysis is run after each batch-wise sieving.

   Microspheres less than 75 µm and larger than 425 µm will be collected as separate fractions and stored for future development purposes.

5. **Vialing and Labelling**

The dry microsphere powder is filled into 20 mL glass vials (200 mg/vial or 500 mg/vial). Currently, the vials are not head-spaced.

Vials are sealed with Teflon stoppers and closed with aluminum crimp seals. There is no outer packaging.

6. Terminal Sterilization

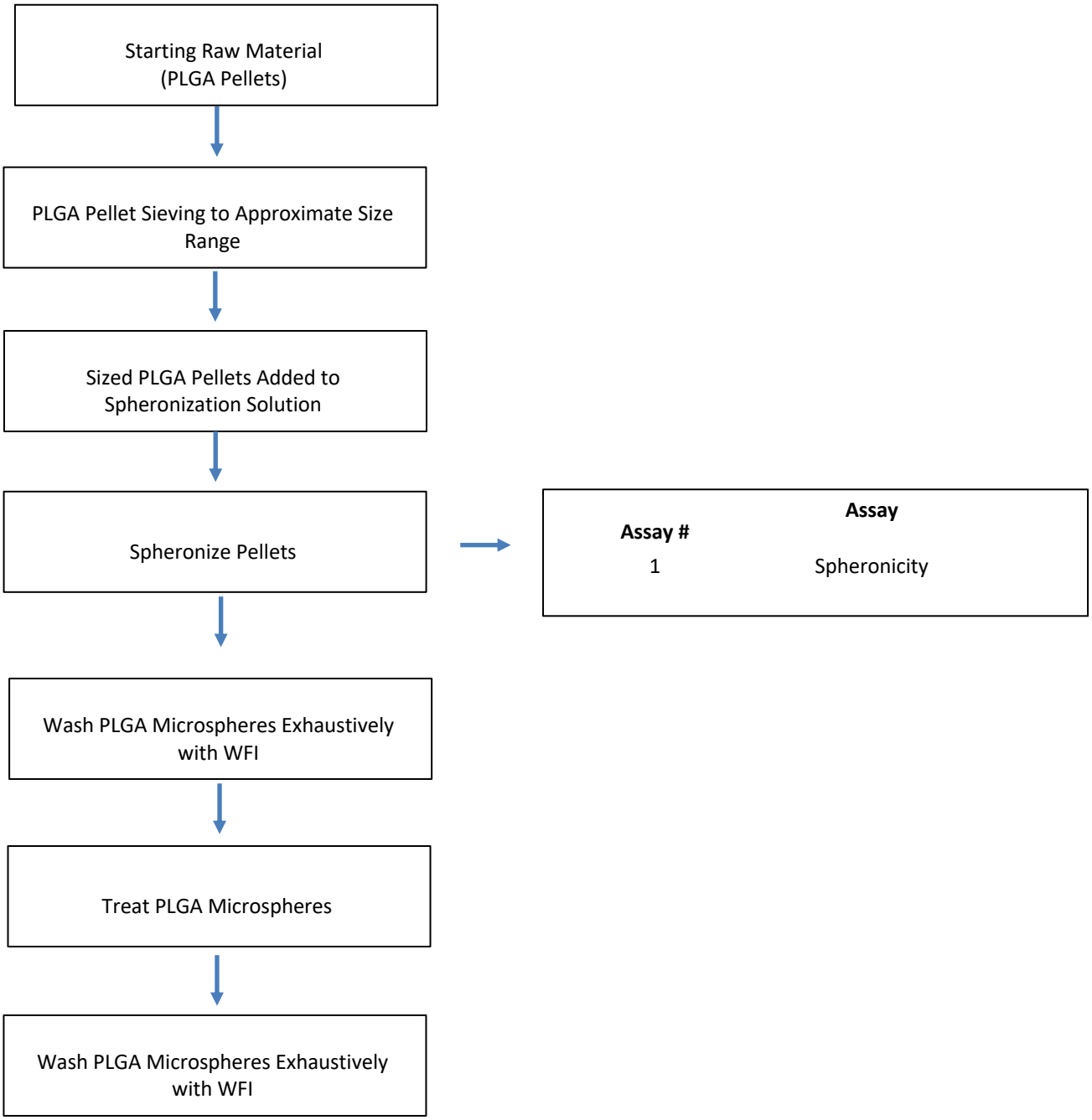
Vialed product is terminally sterilized using gamma-irradiation. The sterilization process has been validated with Steris (Whippany, NY). The sterilization process will be re-validated if a new sterilization provider is used.

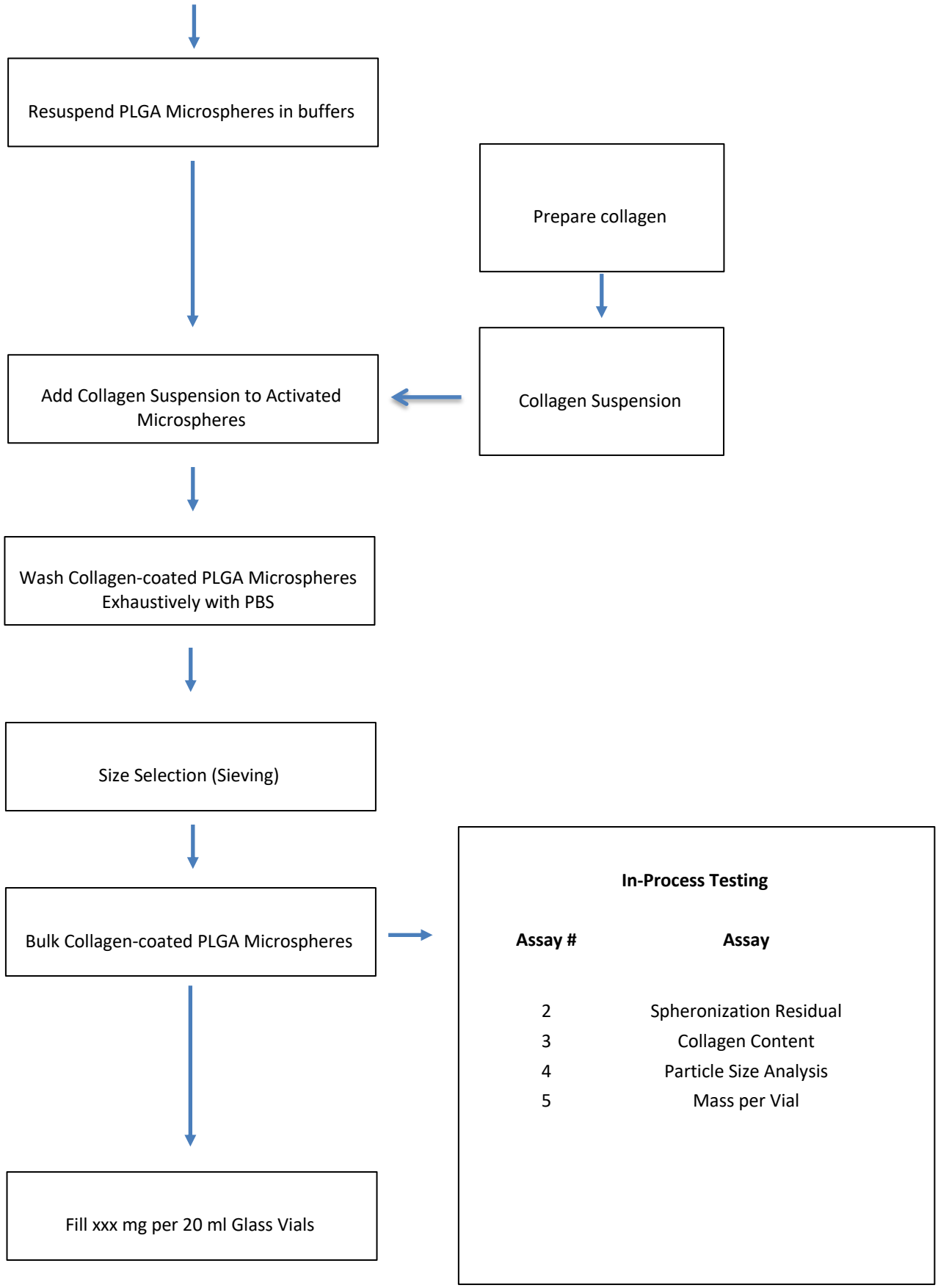
Product is currently stable for 48 months at room temperature.

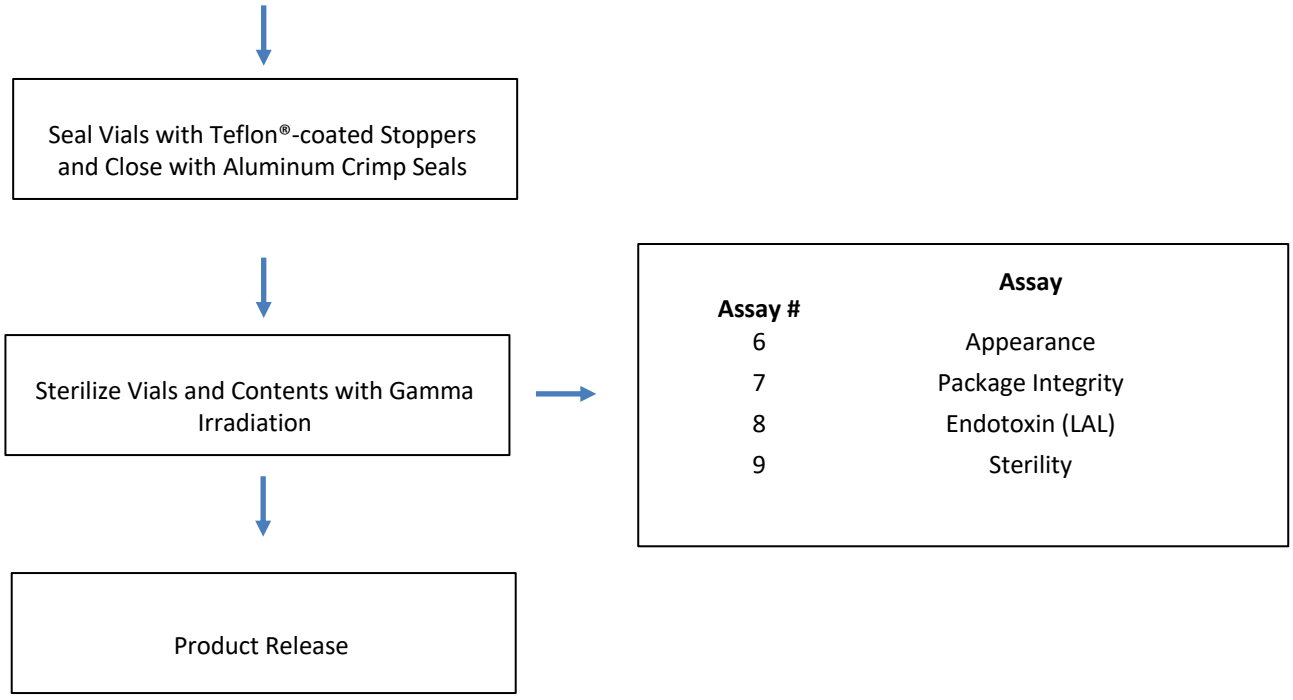
A manufacturing flow process is outlined in Figure 1.

Figure 1. Flow Diagram of Manufacturing Process

Ekobi® Embolization Microspheres Manufacturing Flow Chart




Resuspend PLGA Microspheres in buffers
Prepare collagen
Collagen Suspension
Add Collagen Suspension to Activated Microspheres
Wash Collagen-coated PLGA Microspheres Exhaustively with PBS
Size Selection (Sieving)
Bulk Collagen-coated PLGA Microspheres
Fill xxx mg per 20 ml Glass Vials
In-Process Testing
Assay #
Assay
2
Spheronization Residual
3
Collagen Content
4
Particle Size Analysis
5
Mass per Vial


Seal Vials with Teflon®-coated Stoppers and Close with Aluminum Crimp Seals
Sterilize Vials and Contents with Gamma Irradiation
Product Release
Assay # Assay
6 Appearance
7 Package Integrity
8 Endotoxin (LAL)
9 Sterility

PRODUCT TESTING

The Tables below describe in-process controls (Table 3) and final product release assays and product specifications (Table 4).

IN-PROCESS CONTROLS

Table 2 In-Process Controls and Release Testing

Parameter	**Test Method**	**Specification**
Spheronicity	Microscopy	>99% spherical
Particle Size Analysis	Beckman-Coulter LS 13 320	Conforms to specifications
Mass per vial	Vial Filler	Conforms to specifications (200 mg or 500 mg per vial)
Appearance	Visual	Free-flowing, white to off-white powder, no clumps
Endotoxin	USP	Conforms to specifications
Sterility Assurance	USP	Validated process
Package Integrity	Visual	Vials free of foreign matter; Crimp cap properly fastened (no tears, warps, or other visual defects)

CERTIFICATE OF ANALYSIS

Ekobi® Embolization Microspheres

-
- Spheronization Residual
- Collagen Content
- Particle Size
- Mass per Vial
- Appearance
- Endotoxin
- Sterility Assurance
- Package Integrity

*Note: IMB will perform product release and creation of Certificate of Analysis

ESTIMATED MANUFACTURING NEEDS

To be determined.

SUMMARY OF RFP

IMB is seeking a contract manufacturing organization to manufacture product for clinical and commercial use.

It will be necessary to transfer the manufacturing process to the selected contract manufacturer and perform initial scale-up for commercial manufacturing in 2024. Product manufactured under GMP conditions will be used for commercial sale at the release of the third GMP lot by Q3 2024.

IMB shall retain ownership of all manufacturing processes and of all documentation generated by the CMO in relation to the manufacture of IMB's product. Hard copies of any procedures used to qualify the product will be supplied to IMB. It is IMB's intent to effect transfer of the manufacturing process to a second CMO, as a backup facility.

Please complete all areas of the appended RFP Questionnaire(s), supplying additional information for clarity, where appropriate.

COMPLETED FORMS MUST BE RECEIVED BY: 15 December 2023

CONTACT INFORMATION

Please send the completed forms to:

Attention: Dr. Irwin Griffith
Chief Operating Officer
IMBiotechnologies Ltd.
9650 – 20th Avenue, Suite 215
Edmonton, Alberta
Canada T6N 1G1

Please direct inquiries to:

Dr. Irwin Griffith
780-493-0561
igriffith@imbiotechnologies.com

or

Michael Stewart
780-945-6609
mstewart@imbiotechnologies.com

APPENDIX I - RFP QUESTIONNAIRE – CORPORATE INFORMATION

CORPORATE		
Company Name		
Company Location Head Office Manufacturing Facility(s)		
Company Information Appended	YES ☐	NO ☐
Affiliates	(provide list and location as addendum)	
BRIEF CORPORATE OVERVIEW		
Please provide a brief corporate overview, including year established and number of years your company has been offering contract manufacturing:		
EXECUTIVE RFP RESPONSE		

APPENDIX II – RFP QUESTIONNAIRE – MANUFACTURING

MANUFACTURING		
Manufacture PLGA microspheres capability?	YES ☐	NO ☐
Collagen conjugation capability?	YES ☐	NO ☐
Fill/Finish capability?	YES ☐	NO ☐
Terminal Sterilization capability?	YES ☐	NO ☐
In-Process Testing capability?	YES ☐	NO ☐
Release Testing capability?	YES ☐ Comments:	NO ☐ Comments:
Need for additional equipment	YES ☐ (Please list with justification and cost estimate, as addendum)	NO ☐
Maximum manufacturing capacity per run (vials/run)	_____	
Minimum manufacturing capacity per run (vials /run)	_____	
Maximum number of manufacturing runs per year?		
Storage of Product	YES ☐	NO ☐

Staff Allocation	Please append a staff allocation plan with the background and credentials of the individuals involved and the primary contact for the project. Appended ☐	
Please address how the Cost of Goods can change with time and scale:		

APPENDIX III – RFP QUESTIONNAIRE – REGULATORY

Is the manufacturing facility 21CFR compliant? YES ☐ NO ☐

Is the manufacturing facility ISO 13485:2016 certified? YES ☐ NO ☐

REGULATORY		
FDA Inspection	YES ☐ Date of last inspection: _____ Warning Letters: YES ☐ (If yes, please provide details)	NO ☐ NO ☐
Health Canada Inspection	YES ☐ Date of last inspection: _____ Warning Letters: YES ☐ (If yes, please provide details)	NO ☐ NO ☐
European Inspection	YES ☐ Date of last inspection: _____ Warning Letters: YES ☐ (If yes, please provide details)	NO ☐ NO ☐

APPENDIX IV – RFP QUESTIONNAIRE – MANAGEMENT & REPORTING

PROJECT MANAGEMENT (Please provide a Resume for each team member			
Project Manager:	Name: Phone Number: Email Address:		Resume: ☐
Project Team:	Name:	Title:	☐
	Name:	Title:	☐
	Name:	Title:	☐
	Name:	Title:	☐
	Name:	Title:	☐

PROJECT REPORTING
Please provide descriptions of the reports used for conveying information to the client at each stage of progress, including technology transfer, scale-up and manufacturing. Attach sample reports if at all possible.

APPENDIX V – RFP QUESTIONNAIRE – COST ESTIMATES

COST ESTIMATE		
Cost for Technology Transfer	Comments:	$
Cost of Manufacturing (GMP scale-up Lots in 2024)	Comments: Estimated COG (per vial):	$
Cost of Manufacturing (Commercial Scale)	Comments: Estimated COG (per vial):	$
Equipment Costs	Comments:	$
Documentation Costs	Comments:	$
In-process / Release Testing Costs	Comments:	$
Stability Testing Costs	Comments:	$
Cost for Long Term Storage	Comments:	$
Flow Through Costs	Comments:	$
Others Costs	Comments:	$
TOTAL COST		**$**

APPENDIX VI – RFP QUESTIONNAIRE – REFERENCES

REFERENCES	
Please provide Contact Information for three references	
Reference 1:	Company: Contact Name: Phone Number: E-mail address:
Reference 2:	Company: Contact Name: Phone Number: E-mail address:
Reference 3:	Company: Contact Name: Phone Number: E-mail address:

APPENDIX VII - EVALUATION FACTORS FOR AWARD

Any award to be made pursuant to this RFP will be based upon the proposal with appropriate consideration given to operational, technical, cost, and management requirements. Evaluation of offers will be based upon the CMO's responsiveness to the RFP and the total price quoted for all items covered by the RFP.

The following elements will be the primary considerations in evaluating all submitted proposals and in the selection of a CMO or CMOs:

1. Completion of all required responses in the correct format.
2. The extent to which CMO's proposed solution fulfills IMB's stated requirements as set out in this RFP.
3. An assessment of the CMO's ability to deliver the indicated service in accordance with the specifications set out in this RFP.
4. The CMO's stability, experiences, and record of past performance in delivering such services.
5. Availability of sufficient high quality CMO personnel with the required skills and experience for the specific approach proposed.
6. Overall cost of CMO's proposal.

IMB may, at their discretion and without explanation to the prospective CMOs, at any time choose to discontinue this RFP without obligation to such prospective CMOs.