

TECHNICAL EVALUATION & CDMO FRAME

Allogeneic MSC-EV / Carbomer

MADE technical evaluation and CDMO frame

PI	MAYO SITE	ON NUMBER	MODALITY	VERSION
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PREPARED

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Contents

1	At a glance
2	Program understanding
3	Regulatory position and pathway
4	Starting material
5	Process flow
6	Key equipment
7	Analytical panel and release
7a	Potency
8	Fill, finish and presentation
9	Stability, storage and shipping
10	Comparability
11	Technology transfer approach
12	Indicative timeline
13	MADE experience that supports this
14	Guidance and suggestions
15	Open questions
16	Suggested next step

1. At a glance

Program	Neonatal MSC-derived extracellular vesicle drug substance, compounded with carbomer gel as drug product
Modality	Extracellular vesicles, MSC-derived — inheriting the MSC producer-cell controls
Phase	Phase I/II
Indication and route	Understood to be topical application. Mayo correspondence of 18 August refers to <i>"the EV protocol for atopic dermatitis"</i> — to confirm, see §15
Regulatory status	Product classification not yet confirmed with the agency; no pre-IND or INTERACT meeting recorded in the material we hold — see §3
Starting material	Existing neonatal MSC master cell bank
Drug substance	EVs in 25 mM trehalose storage buffer. 3 L xeno-free bioreactor; filtration to remove cellular debris; TFF buffer exchange. ~17 days from working cell bank through EV collection and vial freeze. Stored at -80 °C
Drug product	Thawed sterile DS combined with sterile Aquasonic 100 carbomer gel through a closed two-syringe Luer-lock system, automated with a high-pressure syringe pump, dispensed into cryovials. Single day. Stored at -80 °C
Where MADE would manufacture	Princeton, NJ, with East Norriton, PA in the MADE network for scale
MADE reference	ON23785-2026
MADE technical fit	Strong on process. One open capability — particle characterization , which needs a defined equivalency bridge before comparability rather than during it. See §7 and §10

This is a technical assessment, not a proposal.

2. Program understanding

Your process generates extracellular vesicles from neonatal MSCs in a 3 L bioreactor under xeno-free conditions. Conditioned media is filtered to remove cellular debris, then tangential flow filtration exchanges into a 25 mM trehalose storage buffer. Drug substance runs approximately 17 days from working cell bank expansion through EV collection, TFF buffer exchange and vial freeze. Drug product is compounded in a single day by combining thawed sterile drug substance with sterile Aquasonic 100 carbomer gel through a closed two-syringe Luer-lock system, automated with a high-pressure syringe pump and dispensed into cryovials. Process development stability has reached ten months at -80 °C on both drug substance and drug product, and is ongoing.

Three design decisions in this process are better than the field norm, and they materially de-risk a transfer.

Xeno-free from the start. Fetal bovine serum contains bovine extracellular vesicles that co-purify with product and are indistinguishable from it by particle counting. Most EV programs manage that problem downstream. Yours designed it out.

TFF rather than ultracentrifugation. The primary go/no-go question for any EV program heading toward commercial scale is whether the isolation method scales. Ultracentrifugation does not; TFF does. Your process is already on the scalable architecture, which removes the largest single process risk most EV programs carry into transfer.

Total protein specified per 10¹¹ particles. That is a particle-to-protein ratio, the most informative purity number available in this modality, and you have it as a release specification rather than as a characterization result.

What the public record adds. There is no approved EV therapeutic, so there is no regulatory template to follow and no incumbent to be measured against. The consequence is that the CMC package this program builds is the argument.

Your priorities, and how MADE answers them

Your priority	How MADE answers it
An isolation architecture that scales	Your TFF-based process is already on the scalable architecture — the transfer preserves it rather than re-engineering it
Xeno-free maintained end to end	Nothing in the transfer reintroduces serum at any step
Particle characterization with a defensible bridge	The particle-measurement question is named, scoped and resolved before comparability, not during it — see §7 and §10
Ten months of stability data protected	Your ongoing stability program continues uninterrupted; transfer-side studies are designed to extend it, not restart it

3. Regulatory position and pathway

Current filing status	Phase I/II. No pre-IND or INTERACT interaction is recorded in the material we hold — Not established, see §15
Designations held	Not established — see §15
Product classification	EVs are typically regulated as biological products rather than as cell therapies in the US or ATMPs in the EU, and the pathway resembles recombinant proteins or vaccines more than it resembles cell therapy in several respects. Confirming this with the agency determines which guidance applies and what the CMC package has to contain
The carbomer question	Whether the carbomer combination is treated as a formulation or as a device component is unresolved, and it changes the filing — see §15
Producer-cell modification	Not applicable here. The producer MSCs are unmodified, so the gene-therapy-derived question that attaches to engineered producer lines does not arise
What the CMC package must support	Phase I/II: the process described with critical parameters identified though not validated; identity, purity, safety and strength defined; a biologically relevant quantitative potency assay, qualified rather than validated; stability sufficient for the proposed storage and shipping, with a real-time study running
What a site change implies	Your RFP sets the requirement directly — comparability of at least three runs using the intended in-house analytical methods, with method validation permitted concurrently, and equivalency demonstrated for any in-house method substituted for one of yours

Applicable guidance	FDA CBER's flexible-CMC position of 11 January 2026 applies to biological products generally. MISEV 2018 and MISEV 2023 are characterization standards, not regulatory requirements, and alignment with them is a statement about characterization completeness rather than about regulatory sufficiency
Indication framing	Our documents describe topical application; Mayo's 18 August correspondence refers to the EV protocol for atopic dermatitis. The two are not the same regulatory framing — endpoints, dose basis and the classification question all turn on which is intended. We are asking rather than assuming

4. Starting material

Source	Existing neonatal MSC master cell bank
Collection	Not applicable — the process starts from an established bank, not from a fresh donor collection
Single-donor or pooled	Not established — see §15
Acceptance criteria	Not established. Bank provenance, passage history and release characterization have not been shared — see §15
Fresh or cryopreserved	Cryopreserved bank; working cell bank thaw begins the ~17-day drug substance cycle
Time from collection to processing	Not applicable for a banked allogeneic starting material
Chain of identity and custody	No per-patient chain of identity is required for an allogeneic banked product. The controls that matter are bank inventory, vial reconciliation and passage tracking
Passage budget	Not established. This is a product-quality control here rather than a housekeeping rule — senescent MSCs produce different EV cargo, and yield and cargo do not necessarily move together. A passage that still yields particles may be yielding different particles
On a failed collection	Not applicable. The equivalent exposure is bank depletion: remaining inventory and the passage budget set how many campaigns the existing bank supports, and both are open questions

5. Process flow

Unit operation	Your approach	MADE capability	Read
Working cell bank thaw and producer expansion	3 L bioreactor, xeno-free	Publicly named platform options include PBS Biotech vertical-wheel, Sartorius Biostat STR, Eppendorf BioFlo 320, Corning CellSTACK and Terumo BCT Quantum Flex	Fits
Conditioning and EV collection	Xeno-free conditioning	The RoosterBio partnership brings chemically defined EV collection media into MADE GMP operations, which removes the serum-vesicle problem at source rather than downstream	Fits, with an option to improve
Clarification	Filtration to remove cellular debris	Standard	Fits

Unit operation	Your approach	MADE capability	Read
Concentration and buffer exchange	TFF into 25 mM trehalose	EV purification by tangential flow filtration is a publicly stated MADE capability	Fits
Polishing	Not specified in the RFP	Column chromatography is a publicly stated MADE capability if a polishing step is required	Available if needed
Sterile filtration	Not specified in the RFP	Standard. The constraint is your size distribution, not the equipment — a 0.22 µm filter excludes anything above 220 nm, so sterile filtration and the sterility assurance strategy are designed together	Design question, see §15
Drug substance fill and freeze	Vial freeze, -80 °C	Standard	Fits
Drug product compounding	Closed two-syringe Luer-lock, syringe-pump automated	Closed aseptic operation, suited to a Grade B / Closed System designation. The work is validating the operation — mixing consistency, dispensing accuracy, minimum fill — rather than performing it	Fits; scope as drug product manufacture, not as fill-finish
Drug product dispense and freeze	Into sterile cryovials, -80 °C	Standard	Fits

On the producer platform. MADE's partnership with RoosterBio, announced 5 May 2026, integrates RoosterBio MSCs, xeno-free expansion media and chemically defined EV collection media into our GMP operations, alongside EV purification by tangential flow filtration and column chromatography. For a program built on an MSC bank, a bioreactor expansion and a TFF purification, that maps almost line for line onto what you already do.

On the compounding step. It is a distinct drug product manufacturing operation with its own excipient controls, its own consistency qualification and its own stability program. It should be scoped that way rather than absorbed into fill-finish, and you have already established that CD73 activity and tetraspanin content evidence batch consistency for it — which gives the validation a defined readout before it starts.

6. Key equipment

Instrument	Your platform	MADE's installed position	Onboarding required
Producer bioreactor	3 L, xeno-free	PBS Biotech vertical-wheel, 6 in service at Princeton (3 MAG and 15 MAG); Sartorius Ambr 15 for small-scale screening, 1 Princeton; Terumo Quantum Flex hollow fiber, 1 Princeton; Sartorius Biostat STR 50 L single-use, 1 East Norriton	Platform selection against your 3 L scale, and a cargo comparison if the scale changes
TFF	TFF into 25 mM trehalose	EV purification by tangential flow filtration is a publicly stated MADE capability. Repligen KrosFlo KR2i units are held at East Norriton in warehouse storage, so the specific skid to be used is to confirm before this program is committed to it	Membrane chemistry and cutoff qualified per process

Instrument	Your platform	MADE's installed position	Onboarding required
Particle concentration and size distribution	MRPS, at four points across your two panels	Particle Metrix ZetaView Evolution quatt (PMX-440-Quatt-C), 1 at Princeton, in service. This is nanoparticle tracking analysis	The one open item. Equivalency bridge against your MRPS dataset, or MRPS at a named partner laboratory — see §7
Tetraspanin identity, bead-based EV flow	Multiplex, CD9 / CD63 / CD81	Beckman Coulter CytoFLEX 13-color, 4 in service at Princeton; Miltenyi MACSQuant, 6 at East Norriton; Agilent NovoCyte Penton, 1 East Norriton	Panel and gating strategy transfer with the method
CD73 functional readout, luminescent output	Plate-based luminescence	Molecular Devices SpectraMax M3, 3 East Norriton; Thermo plate reader, 2; Thermo Varioskan Lux, 1 Princeton	Method transfer, then qualification if reclassified as potency — see §7a
Total protein	BCA	SpectraMax M3 and Thermo plate readers as above; NanoDrop, 1 Princeton and 3 East Norriton	Method transfer
Residual DNA	dPCR	Bio-Rad QX200 ddPCR, 1 Princeton and 4 East Norriton; Thermo QuantStudio, 1 Princeton and 2 East Norriton	Method transfer
Endotoxin	USP <85>	Endosafe, 4 Princeton and 3 East Norriton	EV-matrix interference resolved first — see §7
Mycoplasma	USP <63>	BioFire, 1 Princeton and 2 East Norriton	Standard
Cryogenic freeze	-80 °C vial freeze	Controlled-rate freezers, 2 Princeton and 7 East Norriton, if a controlled rate is required	Freeze profile to confirm — the RFP states -80 °C storage but not the freeze method
Compounding pump and closed Luer-lock set	High-pressure syringe pump, two 60 mL syringes	Not a MADE asset today; the pump and closed-system configuration would be brought in with the operation and qualified as part of it	Equipment specification needed from your team — see §15
Cryo-EM or TEM visualization	Not specified	Outsourced, as is normal in this modality	Vendor selection if required

7. Analytical panel and release

Your proposed panels are thorough, and most of the ten drug substance tests and seven drug product tests sit within MADE's in-house capability.

Attribute	Your method	MADE position	In house or outsourced
DS — Sterility	USP <71>, no growth at 14 days	Direct inoculation suits the matrix; membrane filtration fouls on EV preparations	Outsourced, as standard

Attribute	Your method	MADE position	In house or outsourced
DS — Endotoxin	USP <85>, <0.40 EU/mL	Endosafe in service. EV matrices commonly interfere with the LAL assay and the method needs bridging work — resolve it in Stage 1, not at release	In house, after method work
DS — Mycoplasma	USP <63>, in-process cells at harvest	BioFire in service. Worth extending to conditioned media as well as cells at harvest — testing only the cells misses contamination introduced during conditioning	In house
DS — Pre-dilution particle concentration	MRPS, $\geq 1.5 \times 10^{11}$ particles/mL	ZetaView NTA in service. Different measurement principle — see below	In house, after the bridge
DS — Post-dilution particle concentration and size distribution	MRPS, report results	As above	In house, after the bridge
DS — Tetraspanins CD9 / CD63 / CD81	Multiplex	CytoFLEX and MACSQuant in service; bead-based EV flow is established practice	In house
DS — Appearance	Visual	Standard	In house
DS — Total protein	BCA, $\geq 50 \mu\text{g}$ per 1×10^{11} particles	Plate reader and NanoDrop in service. This is the particle-to-protein ratio, and it is the strongest number on the panel	In house
DS — Functional assay	Luminescent output, $\geq 70\%$, classified <i>Characterization</i>	See §7a	In house
DS — Residual DNA	dPCR, report results	QX200 ddPCR and QuantStudio in service	In house
DP — Sterility	USP <71>	As DS	Outsourced, as standard
DP — Endotoxin	USP <85>, <5 EU/kg per dose	As DS; the carbomer matrix adds its own interference question	In house, after method work
DP — Particle concentration and size distribution	MRPS, report results	As DS, and the carbomer matrix is a second bridging variable — a gel is not a buffer to a particle-sizing instrument	In house, after the bridge
DP — Minimum fill	USP <775>	Standard; also the readout for compounding validation	In house
DP — Tetraspanins	Multiplex, marked <i>Identity (TBD)</i> by your team	Open. A drug product identity attribute that distinguishes compounded product from drug substance is worth defining explicitly — see §15	In house
DP — Appearance	Visual	Standard	In house
DP — CD73 functional assay	Luminescent output, $\geq 70\%$, classified <i>Characterization</i>	See §7a	In house

Attribute	Your method	MADE position	In house or outsourced
Negative markers — calnexin, GM130	Not on either panel	Recommended addition. They demonstrate the absence of cellular contamination, which particle counting and tetraspanin presence cannot detect	In house
Reference EV preparation	Not established	Recommended. With no viability and no cell count in this modality, a qualified reference lot is often the only way to make batches comparable across time	In house

The particle-measurement point, stated precisely. MADE holds a Particle Metrix ZetaView Evolution quatt at Princeton, in service, so particle concentration and size distribution is covered as a capability. The open question is the measurement principle, not the capability. ZetaView is nanoparticle tracking analysis; your panels specify MRPS at four points. The two measure different things — NTA tracks Brownian motion, microfluidic resistive pulse sensing measures a resistive pulse through a constriction — and they do not report identical size distributions on the same preparation. Your RFP invites in-house equivalents where equivalency is demonstrated, so the route is open; it is a bridging study rather than a like-for-like transfer, and we would scope it as analytical work in Stage 1.

Two routes, and we would want your view rather than choose unilaterally: bridge our ZetaView method against your MRPS dataset, or run MRPS with a named partner laboratory at a stated turnaround while the bridge is built.

7a. Potency

Your functional assay is closer to being your potency assay than its classification suggests. The drug substance functional assay at $\geq 70\%$ luminescent output and the drug product CD73 functional assay at $\geq 70\%$ are both classified as *Characterization*, and drug product tetraspanin identity is marked (*TBD*). At Phase I/II that is a defensible position. It is also the position the agency reliably probes as a program moves toward pivotal, and this modality has no default assay to adopt later — there is no EV equivalent of the CAR-T cytotoxicity co-culture or the MSC IDO readout.

The constructive reading is that you have already built the assay you need and have not yet given it the classification it deserves. CD73 is a defensible mechanism-linked attribute for an MSC-derived vesicle, it is already quantitative, it is already specified at $\geq 70\%$, and you already trust it enough to have qualified compounding consistency with it. Converting an existing assay is a far smaller piece of work than building one, and a retained reference EV preparation would complete it.

8. Fill, finish and presentation

There is no aseptic fill-finish operation in this process as it is described. Drug substance is filled into vials and frozen; drug product is compounded and dispensed into cryovials. The compounding step is drug product manufacture in its own right and is treated as such throughout this document.

Drug substance container closure	Vials, frozen at -80 °C. Specification Not established — see §15
Drug product container closure	Sterile cryovials
Fill volume	Controlled by minimum fill, USP <775>, reported rather than specified. Target volume Not established — see §15
Dose form	Carbomer gel — drug substance compounded with sterile Aquasonic 100
Compounding operation	Thawed sterile DS and sterile carbomer passed between two 60 mL syringes through a Luer-lock closed system, automated with a high-pressure syringe pump, then dispensed
Compounding controls	Mixing consistency, dispensing accuracy and minimum fill, with CD73 activity and tetraspanin content as the batch-consistency readouts you have already established
Excipient controls	Aquasonic 100 carbomer specifications and supplier Not established — see §15
Labeling	Not established — see §15
Controlled-rate freeze	Not established. The RFP states -80 °C storage but not whether a controlled freeze rate is applied. Controlled-rate freezers are in service at both MADE sites if one is required
Storage	-80 °C, drug substance and drug product
Post-thaw handling	Thaw approximately 40 minutes at 4 °C; stable for application up to 4 hours at 4 °C, inclusive of the thaw

9. Stability, storage and shipping

Stability status	Process development stability at -80 °C has reached ten months on both drug substance and drug product , and is ongoing
Ongoing expectation	Your RFP expects stability studies on drug substance and compounded drug product annually, unless supported by manufacturing data within the preceding four months
Storage condition	-80 °C for both DS and DP
Stability-indicating methods	Must cover particle count, size distribution, marker expression and potency. There is no viability in this modality, and a program that tracks particle count alone will report a stable product that has lost function
Freeze-thaw tolerance	Not established. The number of permitted cycles has to be fixed and then written into the instruction-for-use in a form a clinical site will follow — see §15
In-use stability	Four hours at 4 °C post-thaw, inclusive of the thaw. Whether that window is supported by data at the intended clinical site conditions is Not established — see §15
Shipper	Not established — see §15
Shipper qualification status	Not established. Shipping qualification is included in the Stage 3 scope below
Chain of custody, outbound leg	Not established — see §15

On protecting what you already have. Ten months of accumulated stability on both DS and DP is an asset, and the transfer should be designed to extend that program rather than restart it. Stability on transfer-side material is additional evidence, not a replacement for yours.

10. Comparability

Your RFP sets the requirement plainly and it is well calibrated: **at least three runs using the intended in-house analytical methods**, with method validation permitted concurrently, and equivalency demonstrated for any in-house method substituted for one of yours. That matches what a transfer of this risk profile should carry.

The analytical bridge is the first piece of work, not the last. Particle characterization sits at four points across your two panels. Settling the ZetaView-to-MRPS question late would rework the analytical plan rather than extend it, which is why it is placed in Stage 1 and gated before the engineering run.

Change to be demonstrated	Risk	Against what, and how
Particle characterization method	Gating	Bridging dataset on shared material, our NTA against your MRPS, with agreed equivalence margins — or MRPS run at a named partner laboratory while the bridge is built
Producer cell bank handling	Medium	Existing neonatal MSC master cell bank transfers; provenance, passage budget and remaining inventory confirmed first
Bioreactor platform	Medium	3 L today. If the platform or scale changes, cargo compared across scale — the product is the cargo
Collection media	Medium	Moving to a chemically defined EV collection medium is an improvement and still a comparability item
TFF membrane and cassette	Medium	Membrane chemistry and cutoff qualified per process
Compounding step	Medium-High	The two-syringe closed system and syringe-pump automation transfer as a validated operation, not as a technique
Analytical methods	Medium	Ten tests across two panels; equivalency demonstrated per method

The CQA set the protocol has to cover. Particle concentration and size distribution; tetraspanin marker profile; calnexin and GM130 absence; particle-to-protein ratio; the functional readout; endotoxin; and sterility and mycoplasma on every lot. A retained reference preparation makes that comparison tractable, which is the second reason to establish one.

11. Technology transfer approach

Stage	What happens	Gate
Stage 0 — technical assessment	This document, the particle-method decision framed, and the questions in §15 put to your team	Indication and classification confirmed before scope is fixed

Stage	What happens	Gate
Stage 1 — paper transfer and gap closure	Batch records mapped; master cell bank provenance, passage budget and inventory confirmed; bioreactor and TFF fit established; carbomer and excipient sourcing qualified; the ten analytical methods gap-assessed, with endotoxin interference resolved first; the particle-method bridge designed	Particle-method decision taken. Endotoxin method suitability demonstrated in the EV matrix
Stage 2 — engineering run	Non-GMP through drug substance and compounded drug product, with producer viability tracked through conditioning and a particle-to-protein ratio established for our process	Engineering run meets your in-process and release specifications
Stage 3 — comparability	Three runs minimum against your specified methods, with method validation concurrent and shipping qualification included	Comparability protocol met on the risk-weighted CQA set
Stage 4 — GMP manufacture, release and supply	GMP campaign, release against the agreed panel, ongoing stability	Formal readiness assessment before GMP activity begins

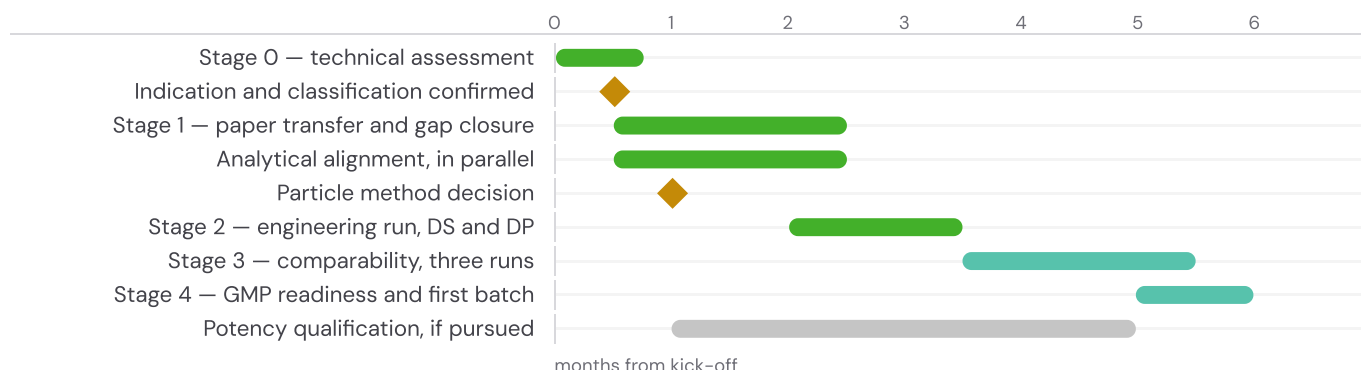
How this becomes a proposal. A MADE proposal presents this plan as numbered work orders grouped into milestones — process establishment and feasibility, process and analytical development, GMP readiness, and GMP manufacture — with each work order carrying its own deliverables, assumptions and exclusions, and Mayo's deliverables stated alongside ours, so both teams always know what the critical path needs next. The first milestone concludes in a joint review of the data with a penalty-free go/no-go decision, and the move from development into GMP activity is a formal stage-gate readiness assessment. The plan above is written to drop into that structure without translation.

12. Indicative timeline

Stage	Duration
Stage 0 — assessment	2–4 weeks
Stage 1 — paper transfer and gap closure	1–3 months
Analytical alignment, in parallel from Stage 1	1–2 months platform-adapted [industry range]
Stage 2 — engineering run	1–2 months
Stage 3 — comparability, three runs	2–3 months
Stage 4 — GMP readiness and first batch	1–2 months
Total, platform-adapted	4–6 months [industry range]
Total, custom	12–18 months [industry range]

Potency qualification, if pursued, runs in parallel and adds 2–4 months to the analytical path [industry range].

On the platform-adapted path:



The particle–method decision is placed early deliberately — it sits at four points across your two panels, and settling it late would rework the analytical plan rather than extend it.

13. MADE experience that supports this

Modality. The RoosterBio strategic technology and supply partnership, announced 5 May 2026, covers scalable MSC and extracellular vesicle manufacturing — off-the-shelf MSCs, xeno-free expansion media, chemically defined EV collection media, and EV purification by tangential flow filtration and column chromatography. MADE has manufactured GMP MSC lots for global customers since technology transfer began in Q3 2025, at approximately 0.5 billion viable cells per CS10. For an EV program the producer–cell track record is the relevant one.

Analytical bench. Flow cytometry, plate-based luminescence and ELISA, ddPCR and dPCR, endotoxin, mycoplasma and particle sizing, all in service across the two sites as set out in §6. Cryo-EM and karyotype outsource, as is normal here.

Sites. Princeton, NJ and East Norriton, PA. Grade B background with Grade A biological safety cabinets for open manipulations; closed-system steps as Grade B / Closed System. EV downstream processing is largely closed; the open steps are formulation and compounding.

Quality. Collective experience from prior organizations across cell therapy quality systems, method qualification, comparability and inspection readiness, including regulatory CMC covering forty-plus products through FDA INDs. This is experience held by individuals now at MADE; the company itself has not yet completed a client audit, and we say so wherever this is described.

14. Guidance and suggestions

Qualify the CD73 luminescent assay as the potency assay and reclassify it — the argument is in §7a. Converting an existing assay is a far smaller piece of work than building one, and it closes the gap that will otherwise be raised for you.

Add a retained reference EV preparation. It is what makes the comparability protocol in §10 tractable. Establishing one now from a well-characterized lot is inexpensive; reconstructing one later is not.

Consider adding negative markers. Calnexin and GM130 demonstrate the absence of cellular contamination, which particle counting and tetraspanin presence cannot detect. A small addition with real assurance value, and it strengthens a MISEV alignment claim.

Resolve endotoxin interference before release testing rather than during it. EV matrices commonly interfere with the LAL assay and method qualification needs bridging work. If your team has already resolved this, we would want the data; if not, it belongs in the transfer plan.

Define drug product identity rather than leaving it TBD. Your panel marks it open, which is an invitation. An identity attribute that distinguishes compounded drug product from drug substance is the thing a reviewer will look for, and it is easier to design now than to retrofit.

Settle the particle-method route early. Either answer works. Leaving it unsettled is what costs time, because it sits at four points across two panels.

15. Open questions

Indication and regulatory framing. Is the indication topical application as our documents describe, or atopic dermatitis as Mayo's 18 August correspondence refers to — and is it the same protocol referenced in the 4 August RFP? Has the product's classification been confirmed with the agency? Is the carbomer combination treated as a formulation or as a device component? Has a pre-IND or INTERACT meeting occurred or been scheduled? Are any designations held?

Producer cells. What is the provenance, passage history and remaining inventory of the neonatal MSC master cell bank? Is it single-donor? What passage budget applies, and has EV cargo been compared across passage?

Process. Is 3 L the intended clinical scale, or is scale-up planned — and if so, has cargo been compared across scale? What is the conditioning duration and cell density? Single or repeated media collection? Is producer viability monitored through conditioning? Is mycoplasma tested on conditioned media as well as on cells at harvest? Is there a sterile filtration step, and how does it sit against your EV size distribution?

Analytics. Would you prefer MRPS transferred, or an equivalent qualified with a bridging dataset? Has endotoxin interference in the EV matrix been assessed? Would you consider reclassifying the CD73 assay as potency? Is there a retained reference EV preparation, and is every lot tested against it? Are negative markers — calnexin, GM130 — assessed anywhere in development, even if not on release?

Drug product and presentation. What defines drug product identity, given the panel marks it TBD? What are the carbomer's own specifications and supplier? What is the target fill volume and the container closure specification? What labeling applies? Is a controlled freeze rate used, or is storage at -80 °C reached passively?

Stability and logistics. How many freeze-thaw cycles are permitted? Is the four-hour post-thaw application window supported by data at the intended clinical site conditions? What shipper and shipping configuration are intended, and what is the chain of custody on the outbound leg?

Program. What dose and application regimen is planned, and how many patients in Phase I/II? What is the target IND date?

16. Suggested next step

A technical call covering three things in order: the indication and classification question, the particle–method decision, and the potency reclassification proposal. We would come having read your RFP in full, so the time goes on decisions rather than on background.