

TECHNICAL EVALUATION & CDMO FRAME

Hepatic-Derived, Kidney-Targeted MSC

MADE technical evaluation and CDMO frame

PI	MAYO SITE	ON NUMBER	MODALITY	VERSION	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	Hepatic-derived, kidney-targeted mesenchymal stromal cell for kidney inflammation
Modality	Mesenchymal stromal cell — a tissue source outside the published characterization envelope
Phase	Development / non-clinical
Regulatory status	Pre-IND. No filing, no designations recorded
Starting material	Hepatic tissue. Autologous or allogeneic is not established — see §15
Drug substance	Not established — see §15
Drug product	Not established — see §15
Where MADE would manufacture	Princeton, NJ
Prior engagement	MADE proposal issued 26 March 2026; the fees in it have since expired and a fresh instrument would be required
MADE reference	ON22345-2026
MADE technical fit	Strong on the science, and the science is the work. Integrated process and analytical development is the right service shape for a program that has not locked its process

This is a technical assessment, not a proposal. We are writing because we think there is a better conversation to be had than a refreshed price.

2. Program understanding

A hepatic-derived mesenchymal stromal cell, targeted to the kidney, for renal inflammation, at development and non-clinical stage. Our March proposal scoped integrated process and analytical development at our Princeton site.

We think this is more scientifically interesting than a generic MSC program, and the interest is also the technical challenge. Bone marrow, adipose and cord-tissue MSCs differ in expansion kinetics, marker expression intensity and functional profile despite all meeting the same identity criteria — the sources are not interchangeable. A **hepatic-derived** MSC therefore sits outside the characterization envelope of essentially every published MSC dataset. That is the point of the program, and it means very little about how this cell behaves can be inferred from the MSC literature. It has to be measured.

Much of the CMC picture below is genuinely undefined, which is what development stage means and is not a criticism. We have written "Not established" wherever that is the true answer rather than filling the space, and each one carries a question in §15.

3. Regulatory position and pathway

Current filing status	Pre-IND, development and non-clinical stage. No filing recorded
Designations held	None recorded
What the CMC package must support	A first-in-human IND. Phase 1 expectations are the process described with critical parameters identified though not validated; identity by flow; viability; sterility, endotoxin and mycoplasma; a biologically relevant, quantitative potency assay that is qualified rather than validated; and stability sufficient for the proposed storage and shipping with a real-time study started. Validated release methods, reference standards and ICH-compliant long-term stability are not required at this stage
Target IND date	Not established — see §15
What a site change implies	Not applicable yet. Nothing is locked, which is precisely why this is the cheapest point to establish the characterization strategy — a change made before the process is fixed carries no comparability burden, and the same change made after a pivotal process is locked is expensive
Applicable guidance	ISCT 2006 minimum criteria; 21 CFR 1271 and 610; USP <71>, <63> and <85>; ICH Q5A. FDA CBER's flexible-CMC position of 11 January 2026 applies: before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected and specifications may be permissive
The recurring modality deficiencies	Donor variability not adequately characterized; potency not correlated to clinical mechanism; senescence characterization insufficient; passage-dependent quality changes not controlled. For a novel tissue source all four start from zero, which makes them cheap to close now and expensive to close later

4. Starting material

Source	Hepatic tissue — outside the standard MSC sources of bone marrow, adipose and cord
Collection	Not established — see §15
Isolation method	Not established — see §15. Enzymatic digestion, explant outgrowth and immunoselection on CD271 or CD146 each carry different purity, timing and regulatory consequences, and for a novel source the choice also shapes what the cell is
Autologous or allogeneic	Not established — see §15. If allogeneic, whether a two-tier master and working cell bank is planned follows immediately from the answer
Acceptance criteria	Not established — see §15
Fresh or cryopreserved	Not established — see §15
Time from collection to processing	Not established — see §15
Chain of identity and custody	Not established — it follows from the autologous or allogeneic answer

Donor variability strategy	Not established, and unmeasured for this source. Two MSC donors meeting identical identity criteria can differ approximately tenfold in functional output; for a novel source that range has simply never been measured
What happens on a failed collection	Not established — see §15

5. Process flow

Unit operation	Your approach	MADE capability	Read
Tissue procurement and receipt	Not established — see §15	Standard receipt with a defined time- and-temperature window to agree	Definable once the source pathway is settled
Isolation	Not established — see §15	Standard, with enzyme residual clearance controlled as part of the process	Fits
Primary culture and expansion	Not established — see §15	Corning CellSTACK-scale flask work, Terumo Quantum Flex hollow fiber, PBS Biotech vertical-wheel, Sartorius Ambr 15 for small-scale screening	Fits. At development scale, flask and CellSTACK work covers the requirement
Cell banking	Not established — depends on autologous or allogeneic	Two-tier master and working cell bank establishment is standard MADE work	Definable once the answer is known
Harvest, wash and concentrate	Not established — see §15	LOVO and CTS Rotea	Fits
Formulation, fill and cryopreservation	Not established — see §15	Controlled-rate freezing and LN2 storage at both sites	Fits. Route of administration will constrain the formulation more than in most modalities

6. Key equipment

At development scale nothing in this program is likely to be gated by equipment. The list below is what would carry the work.

Instrument	Your platform	MADE's installed position	Onboarding required
Corning CellSTACK — multi-layer flask	Not established	Publicly named platform option; a consumable vessel rather than a tracked asset	None
Sartorius Ambr 15 — small-scale screening	Not established	1 at Princeton	None. Useful early for a cell whose expansion kinetics are unknown
Terumo BCT Quantum Flex — hollow fiber	Not established	1 at Princeton	None. The lowest-comparability-risk route out of an open flask process later

Instrument	Your platform	MADE's installed position	Onboarding required
PBS Biotech vertical-wheel	Not established	6 at Princeton	None
LOVO and CTS Rotea — harvest and wash	Not established	LOVO 3 at Princeton, 1 at East Norriton; Rotea 3 at Princeton, 2 at East Norriton	None
Controlled-rate freezer	Not established	2 at Princeton, 7 at East Norriton	None
Beckman Coulter CytoFLEX — flow cytometry	Not established	4 at Princeton, 13-color	Panel design is development work, not onboarding — see §7
SpectraMax M3 and Varioskan Lux plate readers	Not established	3 and 1 respectively across the two sites	None. These carry the IDO, PGE2 and TSG-6 readouts
NucleoCounter and Vi-CELL — count and viability	Not established	NucleoCounter 7 at Princeton; Vi-CELL 2 at East Norriton	None
Endosafe — endotoxin	Not established	4 at Princeton, 3 at East Norriton	None
BioFire — mycoplasma by PCR	Not established	1 at Princeton, 2 at East Norriton	None

7. Analytical panel and release

For a novel-source MSC the standard identity panel is necessary and unusually insufficient. Your cells will very likely meet the ISCT criteria — CD73, CD90 and CD105 positive, CD34, CD45, CD14 and HLA-DR negative — and that will not distinguish them from a bone marrow MSC, from a fibroblast, or from a hepatic stellate cell. The panel below is therefore a starting position for development rather than a release panel.

Attribute	Your method	MADE position	In house or outsourced
Identity, ISCT core	Not established — see §15	Flow on Beckman Coulter CytoFLEX, 13-color. A viability dye and a stated gating strategy are part of the method	In house
Extended identity — tissue origin	Not established — and this is the substance of §14. CD146, CD271 and SSEA-4 offer better specificity than the minimum set, though none is universally accepted	Panel development on the same instrument	In house
Targeting attribute	Not established. Whether this is an identity and potency attribute or a biodistribution observation is an open question — see §14	Depends on the answer	Not established
Viability	Not established	NucleoCounter and Vi-CELL	In house
Sterility	Not established	USP <71>	In house

Attribute	Your method	MADE position	In house or outsourced
Mycoplasma	Not established	BioFire, USP <63>	In house
Endotoxin	Not established	Endosafe, USP <85>	In house
Potency	None in place, so far as we know — see §15	See §7a	In house once developed
Karyotype	Not established	G-banding	Outsourced, as standard
Tumorigenicity	Not established	Standard	Outsourced, as standard
Process residuals and host cell DNA	Not established	ELISA or LC-MS/MS for residuals; qPCR for host cell DNA where enzymatic digestion is used	Residuals outsourced; qPCR in house

7a. Potency

Trilineage differentiation is not a potency assay for an anti-inflammatory indication. It confirms stem-cell character rather than the mechanism, and the agency has raised that repeatedly across MSC programs. For renal inflammation the mechanism-matched candidates are IDO activity, PGE2 secretion, mixed lymphocyte reaction suppression, or — given the hepatic origin and an anti-inflammatory claim — a co-culture readout closer to the target tissue.

No potency assay is established for this program, and for a novel tissue source none can be borrowed from the literature. Complex potency assay development typically adds two to four months to an analytical timeline [industry range], and for a novel-source program it should be assumed necessary rather than hoped against. Building it during development, rather than before a pivotal trial, is the whole argument of §14. The right first question is not "what is your potency assay" but "what do you claim these cells do in the kidney" — the assay follows from the answer, and that answer is yours to give.

8. Fill, finish and presentation

There is no drug product defined yet, so this section is genuinely empty rather than omitted.

Container closure	Not established — see §15
Fill volume	Not established — see §15
Dose form and route	Not established — see §15. Route matters more here than in most modalities: intrathecal and intra-articular delivery tolerate less DMSO and less residual than intravenous infusion, and some routes require a wash-and-resuspend at the clinical site
Labeling	Not established — see §15
Controlled-rate freeze	Not established. Controlled-rate freezers are deployed at both MADE sites when the process needs them

Storage	Not established — see §15
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9. Stability, storage and shipping

Stability status	Not established — see §15. No stability program exists for this cell, and none can be inferred from the MSC literature for a hepatic-derived source
Storage condition	Not established. The modality position for banks is ≤ -150 °C in vapor-phase liquid nitrogen
Stability design MADE would propose	Timepoints at 6, 12, 24 and 36 months, testing post-thaw viability, marker expression and potency , with a loss of more than 10% in viability or potency triggering investigation. Potency stability, not just viability stability — a bank that holds viability but has lost function will produce conforming, ineffective product
Shipper	Not established — see §15
Qualification status	Nothing qualified; nothing yet needs to be
Chain of custody	Not established — it follows from the autologous or allogeneic answer

10. Comparability

There is no comparability exercise here yet, and that is the opportunity rather than a gap. Comparability is what you run when something changes against an established baseline. This program has no established baseline, so the work in front of it is to build one — and every decision taken now is taken for free, where the same decision taken after a pivotal process is locked costs a full comparability package.

The table below is the change inventory as it would stand if the program moved into development with MADE. It is short because so little is fixed.

Change	Risk	Note
Novel tissue source	Highest	No published characterization envelope. Everything is program-specific and must be measured
Potency assay	High	Not established; mechanism-matched development required, and it should be assumed necessary
The "kidney-targeted" mechanism	High	Needs definition as an identity attribute, a potency attribute, or a non-clinical biodistribution observation
Media system	Not established	If serum is in the process, the conversion to human platelet lysate or xeno-free is nearly free now and expensive after a pivotal process is locked
Process maturity	Not established	Expect academic-origin artifacts; academic or research-lab origin normally carries three to five bridging lots when it eventually transfers
Donor variability	High	Unmeasured for this source

11. Technology transfer approach

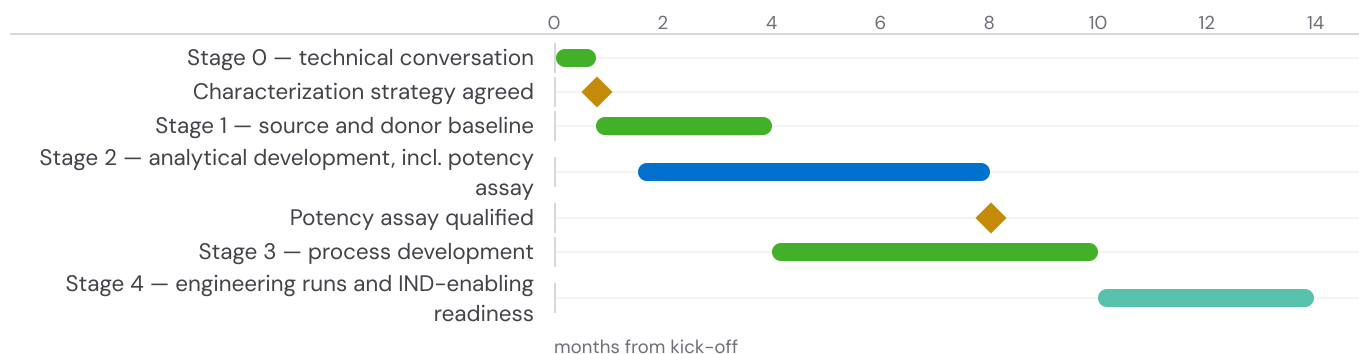
This is integrated development rather than a transfer of a locked process, so the stages are shaped around establishing the baseline rather than reproducing one.

Stage	What happens	Gate
Stage 0 — technical conversation	The three characterization strands in §14 — origin, targeting and mechanism — settled with your group. Questions only your laboratory can answer	Characterization strategy agreed
Stage 1 — source and donor baseline	Expansion kinetics, population doubling time per passage, marker profile across passage, and functional output across donors. Because the source sits outside the published envelope, the program needs its own envelope	Baseline dataset in hand
Stage 2 — analytical development	Extended identity panel evidencing tissue origin; the mechanism-matched potency assay developed and qualified; targeting resolved into an identity, potency or biodistribution attribute	Potency assay qualified
Stage 3 — process development	Culture format, media position, passage and population-doubling limits set and justified. Process and analytical development run together rather than in sequence	Process description with critical parameters identified
Stage 4 — engineering runs and IND-enabling readiness	Non-GMP runs on the destination equipment with destination materials, stability initiated, release panel proposed	Ready for GMP scope

12. Indicative timeline

Because the process is not locked, these are development bands rather than a schedule. They firm up once the Stage 0 conversation has happened.

Stage	Duration
Stage 0 — technical conversation and characterization strategy	Weeks
Stage 1 — source and donor baseline	2–4 months
Stage 2 — analytical development, including potency	Runs alongside Stage 1 and 3; complex potency assay development adds 2–4 months to the analytical timeline [industry range]
Stage 3 — process development	3–6 months
Stage 4 — engineering runs and IND-enabling readiness	2–4 months
Total, custom process with no platform	12–18 months [industry range], plus 2–4 months for academic-origin knowledge transfer [industry range]



The analytical bar is drawn long and started early on purpose. In this modality the analytical gap is usually larger than the process gap, and for a novel tissue source it is larger still.

13. MADE experience that supports this

On MSC manufacture. 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, on platform options including Corning CellSTACK, Sartorius Biostat STR, Terumo BCT Quantum Flex and PBS Biotech vertical-wheel bioreactors.

On integrated development. This is the right service shape for a program that has not yet locked its process — process and analytical development running together rather than in sequence — and it is what our original proposal scoped.

On the analytical bench. The full MSC panel sits in house: identity and extended phenotype on Beckman Coulter CytoFLEX; IDO, PGE2, TSG-6 and mixed-lymphocyte readouts on the SpectraMax M3 and Varioskan Lux plate readers; count and viability on NucleoCounter and Vi-CELL. Karyotype and tumorigenicity are outsourced, as standard.

On quality. MADE's quality leadership carries collective experience from prior organizations across cell therapy quality systems, comparability and method transfer. This is experience held by individuals now at MADE; the company itself has not yet completed a client audit.

On facilities. 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.

14. Guidance and suggestions

Development and non-clinical stage is the cheapest possible point to settle these questions and the most expensive point at which to leave them unsettled. Three strands, and they are the substance of a technical conversation rather than a scope line.

What makes it hepatic. An extended identity panel that evidences tissue origin rather than mesenchymal character alone. CD146, CD271 and SSEA-4 offer better specificity than the minimum set, though none is universally accepted; for a liver-derived population the real question is whether any marker or transcriptional signature separates it from a bone marrow MSC, from a fibroblast, and from a hepatic stellate cell.

What makes it kidney-targeted. Targeting is a mechanistic claim and it needs a readout. If it is conferred by a surface receptor or by engineering, it is an identity and potency attribute. If it is a biodistribution observation, it belongs in the non-clinical package rather than the release panel. The distinction is worth making explicitly rather than carrying it in the program name.

What makes it work. A mechanism-matched potency assay, developed now. See §7a.

Two further recommendations follow from those.

A donor and source characterization baseline. Because hepatic-derived MSCs sit outside the published envelope, the program needs its own: expansion kinetics, population doubling time per passage, marker profile across passage, and functional output across donors. Two MSC donors meeting identical identity criteria can differ approximately tenfold in functional output — and for a novel source, that range is simply unmeasured.

A media position, settled early. Whether the process runs on fetal bovine serum, human platelet lysate or a xeno-free defined medium is not something we know. The regulatory direction is away from serum, particularly in Europe, and a serum-to-xeno-free conversion is a change requiring comparability. At non-clinical stage that conversion is nearly free. After a pivotal process is locked it is expensive.

15. Open questions

The science. What is the tissue source and isolation method? How is the cell distinguished from bone marrow or adipose MSC, and from hepatic stellate cells? **What does "kidney-targeted" mean mechanistically** — an engineered or intrinsic homing property, or a biodistribution observation?

Starting material. Autologous or allogeneic — and if allogeneic, is a two-tier master and working cell bank planned? How is tissue collected, and in what quantity? Fresh or cryopreserved on arrival, and what time and temperature window applies?

Characterization. What identity panel is in use beyond the minimum criteria? Has donor-to-donor functional variability been measured for this source? Is population doubling time tracked per passage? Have passage limits been set, and on what basis?

Potency. What is the claimed mechanism for renal inflammation? Is any functional assay in place, or is characterization currently identity-based? Would you support developing a mechanism-matched assay during the development program?

Process. What culture format and scale today? What media and supplement, and if serum, is a conversion planned? What harvest and wash method?

Drug product. Is a route of administration chosen? What container closure, fill volume and formulation buffer are contemplated? Is any stability data held?

Program. What has changed since March, and what would a proposal need to contain now that the original did not? What is the target IND date? Is the program still funded and prioritized?

16. Suggested next step

A technical conversation on the three characterization strands in §14 — origin, targeting and mechanism. Those are questions only your group can answer, they determine everything downstream, and they are worth an hour regardless of whether a commercial engagement follows.