

PROGRAM TECHNICAL DEEP DIVE

RECLAIM — Allogeneic Adipose MSC Cell Bank

Commercial-grade MCB and WCB for a Phase 3 RMAT cartilage program — technical deep dive

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1. Executive technical summary

This is the most commercially urgent program in the Mayo portfolio and the one closest to a licensed product. RECLAIM is a one-stage cartilage cell therapy combining patient-derived chondrons with **80–90% allogeneic adipose-derived MSCs** from a banked source, currently the subject of an RMAT submission directed toward a BLA ^[S90]. Mayo's internal MSC banks are **nearing expiry and are insufficient for the required scale**, and Mayo is seeking an external CDMO to supply a commercial-grade allogeneic MSC bank.

Dr. Saris stated on 4 August that a partner selection decision is needed within approximately three months to satisfy FDA RMAT documentation expectations ^[S90]. That places the decision in early November 2026.

One remark from that call should shape everything MADE does here. Dr. Saris noted that *how the partner relationship is framed will influence whether the FDA requires full process redevelopment* ^[S90]. That is the single highest-leverage sentence in the Mayo file. A cell bank supplied under one framing is a raw-material change to a program with an existing IND; under another it is a new manufacturing process requiring redevelopment and a much larger comparability burden. The difference is measured in years and in whether the RMAT timeline survives.

MADE should therefore lead with a comparability and regulatory-framing position, not with bank capacity. Bank capacity is table stakes and several CDMOs have it. A partner who arrives with a worked view of how to keep this inside a raw-material change — what comparability dataset supports that framing, what the FDA has accepted in analogous situations, and how the bank is qualified against the existing one — is answering the question Mayo actually has.

The source distinction is deliberate and must not be blurred. The US RECLAIM program uses adipose-derived MSCs, aligned to the current IND. The European IMPACT program uses bone marrow-derived MSCs. FDA and EMA treat these as different drug sources, which also preserves IP differentiation between the markets ^[S90]. Any proposal must be unambiguously adipose. The MSC core is explicit that sources are not interchangeable despite meeting identical ISCT criteria ^[S11] — here that scientific fact is also a regulatory and commercial one.

2. The modality: biology and mechanism

MSCs are plastic-adherent, self-renewing stromal cells isolated from bone marrow, adipose tissue, umbilical cord (Wharton's jelly), dental pulp and other sources. The 2006 ISCT position defined the minimum criteria that still anchor every release panel: plastic adherence, the surface marker profile above, and trilineage differentiation capacity into osteoblasts, adipocytes and chondroblasts ^[S20]. ISCT's 2019 position paper pushed the field toward naming the tissue of origin and the demonstrated function rather than relying on "mesenchymal stem cell" as a category, precisely because the category had become uninformative ^[S21].

The mechanism is paracrine, not structural. In the overwhelming majority of clinical applications MSCs do not engraft and do not differentiate into the target tissue. They act by secreting immunomodulatory, anti-inflammatory, angiogenic and trophic mediators — and increasingly by releasing extracellular vesicles carrying that cargo ^[S21]. This single fact drives most of what follows. If the therapeutic mechanism is secretion, then differentiation capacity is an identity attribute and secretory function is potency, and a program that tests the former as a proxy for the latter has no assurance of function.

Sources are not interchangeable. Bone marrow, adipose and cord-tissue MSCs have different expansion kinetics, different marker expression intensities and different functional profiles, despite all three meeting ISCT criteria ^[S11]. Bone marrow MSC proliferative capacity declines with donor age; cord-derived cells expand faster and further. A source change is a comparability exercise, not a materials substitution.

Donor variability is the defining property of the modality. Two donors meeting identical identity criteria can differ tenfold in IDO and PGE2 output ^[S11]. For an allogeneic product this is managed by qualifying donors on function before committing a bank; for an autologous product it cannot be managed at all, only characterized — which is why autologous MSC programs need wider specifications and a clear position on what happens when a patient's own cells underperform.

3. This program's product, specifically

3.1 The therapy

Product	One-stage cartilage cell therapy — patient chondrons combined with 80–90% allogeneic adipose-derived MSCs
US program	RECLAIM, adipose-derived, aligned to the current IND
European program	IMPACT, bone marrow-derived — a different drug source to both agencies
Drug product	1–2 mL injectable containing 1.6–16 million cells, formulated by mixing chondrons and MSCs into one component of a commercial fibrin gel
Delivery	A 3D-printed third nozzle mount is in development to enable inline mixing during injection
Regulatory status	RMAT submission directed toward a BLA
Indications	Cartilage defects, extending to hip, meniscus, rotator cuff and potentially intervertebral disc — positioned as a platform
SFDC record	Phase 3; molecule RECLAIM; starting material adipose tissue (SVF / lipoaspirate); service category cell bank (RCB/MCB/WCB)
Registered US study	NCT03672825, RECLAIM Phase 1 , 25 subjects, Mayo Clinic sponsor, completed 9 May 2024, PI Aaron Krych. The Phase 3 / confirmatory cohort described on 4 August is not yet registered ^[S92]

Sources: technical call 4 August 2026 ^[S90]; SFDC opportunity ^[S91].

3.2 What MADE is being asked to supply

A commercial-grade allogeneic adipose MSC master and working cell bank, at a scale the existing internal banks cannot reach, replacing banks that are nearing expiry.

This is a narrower and cleaner scope than most of the Mayo portfolio. MADE is not being asked to manufacture the drug product — the chondron combination and fibrin-gel formulation happen at the point of care — but to supply the banked allogeneic component that the drug product is built on.

The autologous half never enters a manufacturing scope at all, and the registered US protocol says so explicitly: the cartilage defect is surgically debrided and the articular cartilage *surrounding the defect rim* is harvested in the same operation, then rapidly digested to release chondrocytes with their pericellular matrix and combined **1:4 with allogeneic adipose MSCs** in fibrin glue ^[S92]. That is the "REcycled" in RECLAIM: the chondrons are recovered from tissue a conventional debridement discards, which is what makes the procedure one-stage — no biopsy, no expansion phase, no second surgery. The European sister program states the same design, at a 10:90 ratio and in Tisseel, with bone marrow-derived rather than adipose MSCs ^[S93].

Two things follow for the bank. **Four cells in five are MADE's material**, so bank sizing is doses × cells per dose × 0.8 and not a fraction to be settled later. And chondron yield is whatever the defect rim gives on the day — surgeon-dependent and lesion-size-dependent — so **the allogeneic bank is the only input in this product that can be specified and held constant**. That is the physical reason the bank's comparability to its predecessor is what carries the accumulated clinical data forward, rather than a regulatory nicety.

That scope has three consequences worth stating. It is **discrete and priceable**, so it can move quickly. It is **the critical path for the RMAT timeline**, because the bank must exist before the confirmatory cohort can run. And it makes MADE a **raw material supplier to a BLA-directed program**, which carries commercial-supply implications well beyond the bank itself.

3.3 The regulatory strategy, as described

Mayo's anticipated approach is to use existing data where possible, with **at most one prospective confirmatory cohort** compared against real-world evidence, conducted with the new cell bank and the new CDMO partner. Device integration — the closed-system processing device now at working-prototype stage — would follow in a subsequent phase ^[S90].

Two implications for the bank. First, the confirmatory cohort is manufactured on the new bank, so the bank's comparability to the existing one is what connects the historical data to the new evidence. Second, because device integration is deliberately sequenced afterwards, the bank work is not blocked by the device program — it can proceed now.

4. Process architecture, unit operation by unit operation

4.1 The chain, end to end

#	Unit operation	Purpose	Where it fails
1	Tissue procurement and receipt	Qualified starting tissue	Shipping window and temperature; donor screening incomplete
2	Isolation	Liberate and select MSCs	Enzyme residuals; fibroblast co-isolation
3	Primary culture and passage to P2–P4	Establish the population	Slow adherence from poor-quality tissue
4	Master cell bank	Single characterized origin for everything downstream	Under-sized bank; incomplete characterization
5	Working cell bank	Manufacturing-ready inventory	Passage budget consumed too early
6	Expansion to scale	Reach dose	Platform change alters phenotype and function
7	Harvest and detachment	Recover cells intact	Enzymatic damage to surface proteins; microcarrier carryover
8	Wash and concentrate	Clear media and residuals	Yield loss
9	Formulation and fill	Cryoprotectant, container, dose	DMSO tolerance at the delivery route
10	Controlled-rate freeze and storage	Preserve function	Post-thaw potency loss, not just viability loss

4.2 Starting material and donor management

The questions that decide a program: is the tissue source defined; are donor qualification criteria defined; single-donor or pooled; what are the procurement logistics and the acceptable time and temperature from collection to processing; is isolation by enzymatic digestion or explant outgrowth; and — the one most often missing — what is the donor-to-donor variability management strategy ^[S9].

For bone marrow, mononuclear cells are separated on a density gradient, plated, and non-adherent hematopoietic cells washed away over the first three to seven days. For cord tissue, explant outgrowth yields a purer population with less fibroblast contamination but takes seven to fourteen days, while enzymatic digestion with collagenase liberates cells in hours and allows same-day plating at the cost of residual enzyme and matrix fragments that need clearing and controlling ^[S21]. Immunoselection on CD271 or CD146 enriches for clonogenic precursors and reduces variability but adds cost and regulatory surface ^[S21].

Passage and population-doubling limits must be defined and justified ^[S9]. This is not paperwork. It is the control that stands between the program and the senescence failure mode.

4.3 Expansion — the decision that carries the most comparability risk

Platform	Character	Typical yield	What it costs you
T-flask, cell factory (CellSTACK, Nunc)	2D, open, manual	Small cohorts, ≤ 10 doses	Labor and footprint — roughly 160 m ² and nine staff for ~100 doses a month; contamination risk from repeated vessel opening ^{[S21][S24]}
Hollow fiber (Terumo Quantum)	2D geometry, closed, automated feed and harvest	$10^7 \rightarrow >10^{10}$ cells in 14–21 days	Fixed vessel geometry; less process visibility ^{[S21][S25]}
Multi-tray and fixed-bed (HYPERStack, iCELLis)	2D geometry, scaled out	600–6,000 cm ² per vessel	Scale-out rather than scale-up
Stirred-tank with microcarriers	3D suspension	$5\text{--}10 \times 10^9$ per 50 L batch, 50–100 doses at 10^8 /dose	The largest phenotype risk — see below ^{[S21][S26]}

Moving from flasks to a stirred tank changes the mechanical environment, and MSCs respond to mechanics. Cells grown on microcarriers under agitation can differ from flask-grown cells in morphology, surface marker intensity and function ^[S11]. Harvest compounds it: enzymatic detachment damages surface proteins, incomplete detachment leaves cells on the carriers and cuts yield, and carrier fragments in the product are a safety concern requiring a clearance step and a test ^[S11]. A 2D-to-3D move is a full comparability exercise and should be planned and priced as one.

Hollow fiber occupies a useful middle position for programs at clinical scale: it is closed and automated, which addresses the contamination and labor problems of flasks, while preserving the 2D growth geometry, which materially reduces the comparability burden of the move ^{[S21][S25]}.

4.4 Media — the choice with the longest regulatory shadow

Fetal bovine serum works, is well characterized, and is where most academic processes start. It also carries xenogeneic contamination risk, real lot-to-lot variability in growth factor content, TSE and BSE considerations, and increasing regulatory pushback, particularly in the EU ^{[S11][S21]}. Human platelet lysate at 5–10% supports equivalent or better expansion and removes the xeno concern, but carries its own lot-to-lot variability; pooling reduces variability at the cost of increased donor exposure ^{[S11][S21]}. Fully defined xeno-free media give the most consistent and most defensible position, historically at the cost of slower growth, though second-generation formulations have narrowed that gap ^[S21].

Treat an FBS-to-xeno-free conversion as a major change, not a materials swap. It shifts growth rate and cell behavior and requires comparability ^[S11]. The right time to do it is before the pivotal process is locked. A program that plans to convert "later" is planning a comparability exercise at the worst possible moment, and REF_09 asks specifically whether a conversion plan exists ^[S9].

4.5 Cell banking

Allogeneic MSC products run a two-tier bank. The master cell bank is established at passage 2–4, typically 50–200 vials at $1\text{--}5 \times 10^6$ cells each, and carries the full characterization burden — identity, purity, viability, sterility, mycoplasma, endotoxin, viral screening, karyotype, tumorigenicity and potency. The working cell bank

derives from a single MCB vial expanded to passage 5–7, typically 200–1,000 vials, with a lighter but still substantial panel [S21].

The arithmetic matters more than it looks. At 10^8 cells per dose and roughly 15-fold expansion per passage, one WCB vial at 2×10^6 cells yields on the order of 45 doses after two passages [S21]. Bank sizing, passage budget and dose count are one calculation, not three, and getting it wrong is discovered late. Clinical passage limits are typically set at P9–P12 to bound senescence and karyotypic drift, and agencies expect demonstration that end-of-production cells retain potency, safety and identity equivalent to early passage [S21].

4.6 Formulation, fill and cryopreservation

The route of administration constrains the formulation more than in most modalities. Intrathecal and intra-articular delivery tolerate less DMSO and less residual than intravenous infusion, and some programs require a wash-and-resuspend at the clinical site — which pushes complexity onto the pharmacy and needs an instruction-for-use written with that in mind. Post-thaw viability specification of $\geq 80\%$ is the common position; the more important question, and the less often asked, is whether post-thaw *potency* has been measured at all [S21].

5. Analytical strategy

5.1 The release panel

Attribute	Method	Typical specification
Identity	Flow: CD73, CD90, CD105, CD34, CD45, CD14, HLA-DR	CD73/CD90/CD105 $\geq 95\%$; CD34/CD45 $\leq 2\%$ [S20] [S21]
Viability	7-AAD, trypan blue or AO/PI	$\geq 80\%$ viable
Sterility	USP <71> direct inoculation, or automated culture	No growth
Mycoplasma	PCR or culture	Negative
Endotoxin	LAL	<2.5 EU/mL for IV; <5 EU/dose
Adventitious viruses	Donor serology; in vitro and in vivo assays at MCB	Negative or non-reactive
Karyotype	G-banding, 20 metaphases, or FISH	Normal diploid
Process residuals	ELISA or LC-MS/MS	FBS protein <50 ng/ 10^6 cells, or HPL limit
Host cell DNA	qPCR	<10 ng/dose where enzymatic digestion is used
Potency	See §5a	Program-specific

Compiled from the MADE MSC modality report's release-panel table, which cites ISCT 2006, 21 CFR 1271 and 610, USP <71>/<63>/<85>, Ph. Eur. and ICH Q5A [S21].

5.2 Where identity testing is weaker than it looks

The ISCT panel is necessary and not sufficient. It does not separate an MSC from a fibroblast, and for an immunomodulatory product tested on identity alone there is no assurance of intended function ^[S11]. CD146, CD271 and SSEA-4 offer better specificity but none is universally accepted, so the practical answer is not a better identity panel — it is a functional potency assay carrying the weight that identity cannot.

Two flow-cytometry practicalities that cause disagreement between sites: a viability dye is essential, because dead cells bind antibodies non-specifically and inflate marker positivity ^[S11]; and the gating strategy — debris exclusion, doublet discrimination, viability gate — is part of the method and must transfer with it.

5a. Potency

5a.1 The trap, stated first

Trilineage differentiation is not a potency assay for an immunomodulatory indication. It confirms stem-cell character. It does not measure the secretory mechanism that is the therapeutic mode of action in most MSC clinical programs, and the FDA has raised this deficiency repeatedly ^{[S4][S1]}. If an RFP names trilineage differentiation as potency, that is a regulatory risk to flag and an alternative to recommend, not a preference to accommodate ^[S9].

5a.2 The assays that do measure mechanism

Assay	Measures	Priority	MADE bench	The pitfall
IDO activity, kynurenine readout	Immunomodulatory potency	Primary for immunomodulation	multi-mode plate reader ^[S4]	Requires IFN- γ stimulation; concentration, duration and cell density change the result dramatically. Standardize or it will not transfer ^[S11]
MLR suppression	Functional immunosuppression	Primary alternative	CytoFLEX + multi-mode plate reader ^[S4]	Responder PBMC donor variability becomes assay variability. Use cryopreserved PBMCs from a single qualified lot ^[S11]
PGE2 secretion	Immunomodulatory mediator	Primary alternative	multi-mode plate reader ELISA ^[S4]	PGE2 is unstable — sample time and temperature change the answer ^[S11]
TSG-6 secretion	Anti-inflammatory mediator	Secondary	ELISA ^[S4]	
VEGF, HGF, IGF-1 secretion	Angiogenic potency	Primary where the MOA is angiogenic	multi-mode plate reader ^[S21]	Mechanism-match required — do not use for an immunomodulatory claim
ISCT identity panel	Identity	Required	CytoFLEX ^[S4]	Necessary, not sufficient

Assay	Measures	Priority	MADE bench	The pitfall
Trilineage differentiation	Stem-cell character	Supportive only	Histology [S4]	Not potency for immunomodulation

Match the assay to the claimed clinical mechanism. An anti-fibrotic program in liver disease is not well served by an IDO assay; a hepatic stellate cell co-culture is closer to its mechanism [S21]. An angiogenic program needs a tube-formation or secretion readout. The right question at first contact is not "what is your potency assay" but "what do you claim these cells do in this indication" — the assay follows from the answer.

IFN- γ licensing is worth understanding as a process lever, not only an assay condition. MSC immunomodulatory output is inducible; priming changes it. A program that primes in manufacture and a program that does not are making different products, and the potency assay has to reflect which one is being dosed.

5 (continued) — Comparability is the product

For most programs in this package the analytical discussion is about what the release panel should contain. Here it is about something more specific: **what dataset persuades the FDA that a new bank from a new manufacturer is the same drug source as the old one.**

5.1 The bank characterization scope

A commercial-grade two-tier bank carries a heavy characterization burden, and for a BLA-directed program it is heavier still. The MSC core sets out the scope: at MCB, identity, purity, viability, sterility, mycoplasma, endotoxin, viral screening, karyotype, in vitro tumorigenicity and potency; at WCB a lighter but substantial panel [S21]. Stability at 6, 12, 24 and 36 months under vapor-phase liquid nitrogen, testing post-thaw viability, marker expression **and potency** [S21].

5.2 The comparability dataset that matters

The question is not whether the new bank meets specification. It is whether it is equivalent to the bank the existing clinical data was generated on. That argues for a head-to-head design against retained material from the expiring banks, if any remains — **and if it does, securing it before it expires is urgent and should be raised immediately.**

The MSC core's CQA priorities apply: identity and purity HIGH; **immunomodulatory or mechanism-matched functional activity CRITICAL**; viability HIGH; proliferative capacity HIGH; karyotype MEDIUM and rising with passage; population doubling time as the cheapest senescence signal [S5][S11].

5.3 The potency question, sharpened by the indication

RECLAIM's mechanism is not primarily immunomodulation. The MSCs are combined with chondrons in a cartilage repair procedure, where the plausible contributions are trophic support of chondrogenesis and matrix production rather than immune suppression.

That matters because the MSC core's default potency recommendations — IDO, PGE2, MLR suppression — are matched to immunomodulatory indications and would be **mechanism-mismatched here** ^[S4]. The core is equally explicit that trilineage differentiation is not a potency assay for immunomodulatory programs; for a cartilage program, chondrogenic capacity is closer to the mechanism, though it should be justified as mechanism-matched rather than adopted because it is the familiar ISCT assay.

This is a substantive technical question to put to Dr. Saris's team rather than to answer unilaterally: what potency attribute does the existing IND carry, and does it need to carry more weight for a BLA? At Phase 3 the answer largely exists already, and aligning to it is the priority.

5.4 Donor variability at commercial scale

Two donors meeting identical identity criteria can differ tenfold in functional output ^[S11]. For a commercial bank supplying a licensed product, donor qualification on function — not just on identity — before bank commitment is the control that prevents an expensive discovery later. Whether Mayo qualified its existing donors this way, and on what assay, is worth knowing.

6. Comparability and technology transfer

6.1 Transfer risk

The risk matrix is modality-independent: academic or research-lab origin is HIGH risk with three to five bridging lots and equivalence margins on CQAs; another CDMO is MEDIUM with two to three lots; MADE development to MADE GMP is LOW-MEDIUM with one to two ^[S5]. Most Mayo MSC programs are academic-origin, which sets the expectation honestly at the start.

6.2 The changes that carry real risk in this modality

Change	Risk	Why
2D flask to 3D microcarrier	Highest	Mechanical environment, morphology, marker intensity, function, plus a new harvest mechanism and a carrier-clearance requirement ^[S11]
FBS to hPL or xeno-free	High	Growth rate and cell behavior shift; regulatory position improves but comparability is required ^[S11]
Tissue source change	High	Sources are not interchangeable despite meeting the same identity criteria ^[S11]
Donor or bank change	High	Tenfold potency range between qualifying donors ^[S11]
Flask to hollow fiber	Medium	Closed and automated, but 2D geometry preserved — the lowest-risk route to closed manufacturing ^[S21]
Passage extension	Medium	Senescence and karyotypic drift; needs end-of-production equivalence data ^[S21]

6.3 The CQA set a comparability protocol must cover

Identity by flow and purity at HIGH priority; **immunomodulatory activity by IDO, PGE2 or MLR at CRITICAL**; viability HIGH; proliferative capacity HIGH; karyotype MEDIUM and rising with passage; endotoxin HIGH; sterility and mycoplasma required every lot ^[S5]. Add population doubling time, which is the cheapest early senescence signal available and the one most often not tracked ^[S11].

6.4 The staged plan MADE runs

Stage 0 — technical assessment. Read the process against the modality checklist, name what is defined and what is assumed, produce the sponsor clarification list.

Stage 1 — paper transfer and gap closure. Documentation review, equipment fit, materials sourcing and qualification, analytical gap assessment. In this modality the analytical gap is usually larger than the process gap, so it starts first, not second.

Stage 2 — engineering run. Non-GMP on destination equipment with destination materials, and — specific to MSC — with population doubling time tracked per passage, so the senescence question has data behind it before GMP.

Stage 3 — comparability. Head-to-head on the risk-weighted CQA set, with functional potency carrying the weight.

Stage 4 — GMP manufacture and release.

6 (continued) — The engagement

6.1 Timing

Partner decision needed	Approximately three months from 4 August 2026 — early November ^[S90]
Driver	FDA RMAT documentation expectations
Existing banks	Nearing expiry, insufficient for required scale
Next step agreed on the call	Julie Allickson to send the Mayo RFP package, supplemented with scientific publications, Mayo videos and patient education materials; MADE to review and prepare creative manufacturing and cell bank options ^[S90]

As of this document the RFP has not been received. Chasing it is the immediate action, and the technical package here is a reason to make that contact rather than a passive wait.

6.2 Risk inventory

Item	Risk	Note
Regulatory framing of the partnership	Highest	Determines whether FDA requires full process redevelopment ^[S90]

Item	Risk	Note
Comparability to the expiring banks	Highest	Retained material may be the only bridge; secure it before expiry
Source fidelity — adipose, not bone marrow	High	Different drug source to FDA and EMA; also IP differentiation [S90]
Potency attribute alignment to the existing IND	High	Mechanism is chondrogenic and trophic, not immunomodulatory
Donor qualification for a commercial bank	High	Functional qualification before commitment [S11]
Bank sizing against commercial demand	Medium-High	Dose is 1.6–16 million cells across a platform of indications
Timeline against RMAT documentation	High and dated	Early November decision

6.3 Staged plan

Stage 0 — technical assessment and regulatory framing. This document plus a worked position on comparability framing. Weeks, and it is what the November decision needs.

Stage 1 — donor sourcing and qualification. Adipose donor identification and functional qualification, with acceptance criteria agreed against the existing bank's profile.

Stage 2 — MCB establishment and full characterization, including tumorigenicity, karyotype and viral safety.

Stage 3 — WCB establishment and comparability against retained material from the existing bank where available.

Stage 4 — stability program initiation and commercial supply planning, with the confirmatory cohort supplied from the new bank.

7. Stability, storage and logistics

Master and working cell bank stability are assessed at 6, 12, 24 and 36 months under storage at $\leq -150^{\circ}\text{C}$ in vapor-phase liquid nitrogen, testing post-thaw viability, marker expression and potency; a loss of more than 10% in viability or potency triggers investigation and possible disqualification of affected vials [S21].

The point worth pressing: **potency stability, not just viability stability.** A bank that holds 80% viability at 36 months but has lost immunomodulatory output is a bank that will produce conforming, ineffective product. Programs that only monitor viability have not tested the thing that matters.

Dose ranges across the modality span four orders of magnitude, roughly 10^5 to 10^9 cells, driven by indication, route and source — $1\text{--}2 \times 10^6$ cells/kg intravenously for acute GVHD, $1\text{--}10 \times 10^7$ per dose intra-articularly for knee osteoarthritis, 120×10^6 locally for Crohn's perianal fistula, $1\text{--}2 \times 10^7$ intrathecally for spinal cord injury [S21][S27]. Weight-normalized dosing predominates where organ mass scales with body weight; fixed doses are usual for

local injection. Only about 39% of published MSC trials compared more than one dose cohort, so dose-response is generally uncharacterized across the field ^[S27] — which means a program's chosen dose is often empirical, and that is worth knowing before designing a process around hitting it exactly.

8. Supply chain and critical materials

Category	Material	Typical source	Risk
Starting material	Bone marrow, adipose or cord tissue	Donor collection or tissue bank	MEDIUM — donor variability is inherent, not a supply failure ^[S6]
Isolation	Collagenase, hyaluronidase	Worthington, Nordmark and others	LOW — GMP grade from multiple sources ^[S6]
Media supplement	Human platelet lysate	Compass Biomedical, STEMCELL, Macopharma	MEDIUM — lot-to-lot variability; pooling trades variability for donor exposure ^[S6]
Media supplement	FBS	Multiple	LOW on supply, HIGH on regulatory — the trend is away from it ^[S6]
Media	Xeno-free defined formulations	Multiple commercial suppliers	LOW-MEDIUM — qualification per formulation
Growth factors	FGF-2, EGF, PDGF	Multiple	LOW-MEDIUM
Bioreactor	Microcarriers	Cytiva, Corning, SoloHill	MEDIUM — the specific carrier type requires qualification and is not substitutable ^[S6]
Cryo	DMSO-based cryoprotectant	BioLife and others	LOW-MEDIUM

Unlike CAR-T, this modality has no single dominant supply risk on the scale of viral vector. The risk is distributed and biological: the tissue donor, the platelet lysate lot, the microcarrier surface chemistry. Each is individually manageable and collectively the reason incoming material performance testing earns its place.

9. Regulatory and CMC

9.1 The four deficiencies that recur

1. Donor variability not adequately characterized
2. Potency assay not correlated to the clinical mechanism — commonly trilineage differentiation
3. Senescence characterization insufficient
4. Passage-dependent quality attribute changes not controlled

Source: FDA deficiency patterns by modality ^[S1]. All four are the same underlying problem: the product is defined by what it is rather than by what it does. A CDMO can materially close all four, and doing so early is far cheaper than doing so under pivotal pressure.

9.2 Phase-appropriate expectations

Phase 1 needs the process described with critical parameters identified though not validated; identity by flow; viability typically above 70%; sterility, endotoxin and mycoplasma; a biologically relevant, quantitative potency assay that is qualified rather than validated; and stability sufficient for proposed storage and shipping with a real-time study started. It does not need validated release methods, reference standards or ICH-compliant long-term stability ^[S1].

The January 2026 flexible-CMC position applies here as it does everywhere: before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected, specifications may be permissive, and there is no requirement for three PPQ lots ^[S12]. MSC RFPs from academic sponsors are frequently over-specified against the sponsor's actual phase, and right-sizing that is real value ^[S1].

9.3 The xeno-free direction

Regulatory expectation is moving away from FBS, most firmly in the EU ^{[S9][S21]}. A program planning a pivotal trial on FBS-supplemented media should have a conversion plan with a comparability strategy attached, and should run the conversion before the process is locked rather than after.

10. Clinical and technical precedent

10.1 The modality is approvable

On 18 December 2024 the FDA approved Ryoncil (remestemcel-L-rknd), an allogeneic bone-marrow MSC therapy, for steroid-refractory acute graft-versus-host disease in patients from two months of age — the first FDA-approved MSC therapy. Efficacy rested on MSB-GVHD001 (NCT02336230), a single-arm, multicenter study in 54 pediatric patients ^[S22]. After a long drought of approved MSC products in the United States, this is the existence proof that the regulatory path closes.

10.2 And a promising small trial is not a product

On 13 December 2024, five days earlier, the European Commission withdrew the marketing authorization for Alofisel (darvadstrocel) — allogeneic expanded adipose MSCs for complex perianal fistulas in Crohn's disease — at Takeda's request ^[S23]. The original ADMIRE-CD study in 212 patients had shown a 15.8% difference over placebo in combined remission at 24 weeks ^[S28]. The confirmatory ADMIRE-CD II study in 568 patients showed **2.4%**, missing its primary endpoint and every secondary endpoint ^[S23].

No new safety signal was identified. This was not a toxicity failure; it was an efficacy failure on replication at scale.

The manufacturing reading of that outcome is the one worth carrying into any MSC program. Product consistency — donor-to-donor functional variability, potency drift across passage and bank, mechanism-mismatched potency assays that cannot detect any of it — is a leading hypothesis for why an effect that looked real in 212 patients did not hold in 568. It does not prove the mechanism is wrong. It does mean that a program which cannot measure its own product's function is running a risk it cannot see, and that the analytical work described in §5a is not a compliance exercise but the thing that makes a pivotal result interpretable.

10.3 The field's own pattern

Dose-response is largely uncharacterized: about 39% of MSC trials compare more than one dose cohort ^[S27]. Route-dependent bioavailability differs by orders of magnitude — intravenously administered MSCs are substantially trapped in the pulmonary capillary bed, which is why locally delivered programs and systemically delivered programs are not comparable on dose. And the modality's approvals to date are in indications where the immunomodulatory mechanism is closest to the clinical endpoint.

11. MADE capability against this modality

11.1 Process equipment — evidenced

Two sources agree here, and one of them is public. The internal equipment inventory evidences **Terumo Quantum Cell Expansion**, Sepax cell processing, Xuri W25 rocking bioreactor, KrosFlo TFF, BIOSTAT B-DCU II, controlled-rate freezing and LN2 storage ^[S8]. The RoosterBio partnership announcement of 5 May 2026 — public, and therefore already sayable — names the manufacturing platform options as **Corning CellSTACK, Eppendorf BioFlo 320, Sartorius Biostat STR, Terumo BCT Quantum Flex and PBS Biotech vertical-wheel bioreactors**, with flask production supported to 40×CS10 scale and single-use bioreactor tech transfer advancing toward client readiness ^[S33].

Terumo Quantum is the directly relevant one. Hollow-fiber expansion is the lowest-comparability-risk route from an academic flask process to closed, automated clinical manufacture — it removes the contamination and labor exposure of open flask work while preserving 2D growth geometry, so the cells are not simultaneously being asked to tolerate a new mechanical environment ^{[S21][S25]}. For a Mayo program currently running flasks, this is a real and specific answer rather than a generic capability claim.

11.2 Process equipment — evidenced against the registers

Verified 23 August 2026 against both site registers, with qualification status attested by MADE operations on the same date ^[S8].

REF_O9 fit-check item	In service	Detail
Terumo Quantum Flex — hollow fiber	1	Princeton. The lowest-comparability-risk route out of an academic flask process
Sartorius Biostat STR — stirred tank	1	East Norriton, 50 L single-use, in V-018

REF_09 fit-check item	In service	Detail
Sartorius Ambr 15 — small-scale screening	1	Princeton
PBS Biotech vertical-wheel	6	Princeton — 3 MAG and 15 MAG
Eppendorf BioFlo 320, to 40 L	attested	Held per MADE operations, 23 August 2026; absent from both registers
LOVO — harvest and wash	4	3 Princeton; 1 East Norriton in L-140
CTS Rotea — harvest and wash	5	3 Princeton; 2 East Norriton
Xuri / WAVE W25 rocking	21	East Norriton, in L-140 and P-182
Sartorius Biostat B-DCU II	—	4 Princeton, Inactive
Terumo Quantum, original	—	1 Princeton, Inactive; superseded by the Quantum Flex
iCELLis — fixed bed	—	Not held. The only REF_09 MSC fit-check item MADE does not have

The expansion fleet spans screening (Ambr 15), hollow fiber (Quantum Flex), vertical-wheel (3 L and 15 L), rocking bag (Xuri) and stirred tank to 50 L (Biostat STR), with BioFlo 320 to 40 L alongside. iCELLis is the single genuine absence, and there is no MSC expansion requirement across that range that needs it.

The public track record sits alongside it. 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 ^[S33].

11.3 Analytical bench — evidenced against the registers

Verified 23 August 2026 against the Princeton register (464 assets) and the East Norriton register (1,530 assets), with qualification status attested by MADE operations on the same date ^[S8].

Need	Instrument	In service
Identity, purity, phenotype, exhaustion panel	Beckman Coulter CytoFLEX, 13-color	4 Princeton
Additional flow capacity	Miltenyi MACSQuant Analyzer; Agilent NovoCytte Penteon; Nexcelom image cytometer	6, 1 and 2 respectively, East Norriton, in L-135 and L-141
Rapid in-process flow	Accellix cytometer	1 East Norriton, in L-141
Cytotoxicity, cytokine and ELISA readouts	Thermo Varioskan Lux; Thermo plate reader; Molecular Devices SpectraMax M3	1, 2 and 3 respectively — Princeton and East Norriton L-135/L-141
Vector copy number, editing efficiency	Bio-Rad QX200 ddPCR	1 Princeton, 4 East Norriton in L-138 and L-144
Orthogonal dPCR	Thermo QuantStudio	1 Princeton, 2 East Norriton
Count and viability	NucleoCounter NC-200	7 Princeton
Count and viability	Beckman Vi-CELL	2 East Norriton, in V-018 and V-019

Need	Instrument	In service
Particle concentration and size	Particle Metrix ZetaView Evolution quatt	1 Princeton
Mycoplasma	BioFire	1 Princeton, 2 East Norriton
Endotoxin	Endosafe	4 Princeton, 3 East Norriton
Nucleic acid quantitation	NanoDrop	1 Princeton, 3 East Norriton
Colony counting (CFU)	Reichert colony counter	1 East Norriton, in V-042
Hematology differential	Sysmex XN-330	held at East Norriton, in storage

11.4 Manufacturing environment

Princeton, NJ and East Norriton, PA. Grade B background with Grade A BSC for open manipulations; closed-system steps described as Grade B / Closed System. Open flask work in an MSC process is precisely the manipulation that drives the case for moving to a closed platform.

11.5 Team experience

MADE's quality leadership carries collective prior-organization experience across cell therapy quality systems, comparability and method transfer — including IND approval work on an MSC-adjacent program (FCR001) at Bristol Myers Squibb, quality risk management and inspection-readiness programs at Adaptimmune and GSK, and regulatory CMC leadership covering forty-plus products through FDA INDs at Halloran and Minaris. This is prior-organization experience held by named individuals now at MADE. MADE itself has not yet completed a client audit, and that distinction is stated wherever this is described to a client.

11.6 Indicative economics and duration

Custom process, no platform	12–18 months, kick-off to first released GMP batch ^[S2]
Platform-adapted process	4–6 months ^[S2]
Academic-origin process	add 2–4 months to knowledge transfer ^[S2]
Complex potency assay development	add 2–4 months to the analytical timeline ^[S2]

Industry-standard scoping ranges for directional use. Not MADE pricing until finance has scoped the program ^[S2]. Note that the potency-development modifier applies to most MSC programs coming out of an academic lab, and should be assumed present unless the sponsor demonstrates otherwise.

12. Open questions for Dr. Saris's team

Regulatory framing — ask first. How does Mayo intend to frame the CDMO relationship in the RMAT submission, and what has the FDA indicated about whether a new bank constitutes a raw-material change or triggers process redevelopment? What comparability package does Mayo believe supports the narrower

framing?

The expiring banks. When exactly do the current banks expire? **Is retained material available for head-to-head comparability, and can it be secured before expiry?** What donor qualification was performed on the existing banks, and on what functional assay?

Source and process. What adipose source and isolation method underpins the current bank? What media and supplement — and if FBS, is a conversion contemplated before BLA? What passage budget applies, and what end-of-production equivalence data exists?

Potency. What potency attribute does the current IND carry? Is it mechanism-matched to a cartilage-repair indication, and does Mayo expect it to need strengthening for a BLA?

Scale and supply. What annual dose volume is anticipated across the platform indications? Given 1.6–16 million cells per 1–2 mL dose, what bank size does that imply? Is MADE being asked for the bank only, or for the bank plus ongoing commercial supply?

Program. When will the RFP package arrive? Which other CDMOs are in the process? Does the closed-system device phase change the bank requirement when it arrives?

13. Sources

Tag	Source
[S1]	REF_01 — Regulatory Intelligence Knowledge Base (MADE internal, proposal-generator appraisal engine)
[S2]	REF_02 — COGS and Timeline Modeling Framework (MADE internal)
[S4]	REF_04 — Potency Assay Strategy Advisor (MADE internal)
[S5]	REF_05 — Comparability and Tech Transfer Planning Framework (MADE internal)
[S6]	REF_06 — Supply Chain and BOM Risk Analysis Framework (MADE internal)
[S8]	MADE internal capability inventories — Equipment_List_from_BMRAM.xlsx and List_of_Analytical_Instruments_at_Made_Scientific_Feb_2026.xlsx, as specified in proposal-generator design.md §4.8. The xlsx files were not available to this machine; instrument names come from that specification and must be confirmed against the BMRAM export before client use.
[S9]	REF_09 — Modality-Specific Evaluation Depth Checklists, Modality 3 (MADE internal)
[S11]	REF_11 — Cell Therapy Manufacturing and Analytical Deep Knowledge v2.0 (MADE internal)
[S12]	FDA CBER, Flexible CMC Requirements announcement, 11 January 2026
[S20]	Dominici M et al. Minimal criteria for defining multipotent mesenchymal stromal cells. Cytotherapy 2006. PMID 16923606
[S21]	MADE MSC modality research report, PROJ-047 bibliographer — chapters 1 (biology), 7 (potency and mechanism assays), 8 (dosing, routes and stability), 9 (CMC, manufacturing and quality control), 10 (regulatory). Compiled with primary citations; DOIs and PMIDs are carried in the source chapters
[S22]	FDA, approval of remestemcel-L-rknd (Ryoncil) for steroid-refractory acute GVHD in pediatric patients, 18 December 2024; Summary Basis for Regulatory Action

Tag	Source
[S23]	European Medicines Agency, Alofisel withdrawn from the EU market, 13 December 2024; ADMIRE-CD II outcome
[S24]	Schirmaier C et al. Scale-up of MSC expansion. Stem Cells Translational Medicine 2014. DOI 10.5966/sctm.2013-0146
[S25]	Lock LT et al. Quantum hollow-fiber MSC expansion. Cytotherapy 2017. DOI 10.1016/j.jcyt.2017.09.004
[S26]	Mizukami A, Swiech K. Mesenchymal stromal cells: from discovery to manufacturing. Frontiers in Bioengineering and Biotechnology 2018. DOI 10.3389/fbioe.2018.00121
[S27]	Renesme L et al. Establishment of a consensus definition and reporting of MSC dosing. Stem Cells Translational Medicine 2022. DOI 10.1002/sctm.21-0289
[S28]	Panés J et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: ADMIRE-CD. Lancet 2016. PMID 27477896
[S33]	Made Scientific and RoosterBio announce strategic technology and supply partnership to expand scalable MSC and extracellular vesicle manufacturing. madescientific.com/news, published 5 May 2026. Publicly disclosed and therefore quotable
[S90]	Fellow AI notes, "Mayo Clinic Made Scientific-MS-C", 4 August 2026 — introductory technical call. Attendees included Dr. Daniel Saris and Dr. Julie Allickson for Mayo. Records the RECLAIM/IMPACT source distinction, the 80–90% allogeneic MSC composition, the 1–2 mL / 1.6–16 million cell drug product in commercial fibrin gel, the closed-system device at prototype stage, the three-month partner-decision requirement, and the observation that partnership framing influences whether FDA requires process redevelopment. Fellow diarization is unreliable on this recording — attributions are by content
[S91]	Salesforce opportunity 23555-2026, Phase III MSC MCB & WCB manufacturing; stage Engaged; phase PH-3, molecule RECLAIM, starting material adipose tissue (SVF / lipoaspirate), service category cell bank (RCB/MCB/WCB), primary contact Daniel Saris; retrieved 2026-08-22
[S92]	ClinicalTrials.gov NCT03672825 — <i>RECLAIM: A Phase I Safety and Feasibility Trial of REcycled CartiLage Auto/Allo Implantation</i> , Mayo Clinic, completed 9 May 2024, PI Aaron Krych. Retrieved via the API 2026-09-03
[S93]	ClinicalTrials.gov NCT04236739 (IMPACT2) and NCT02037204 (IMPACT), UMC Utrecht — defect-derived autologous chondrons with allogeneic MSCs at 10:90 in Tisseel. Retrieved 2026-09-03
[S92]	MAYO-CELL-THERAPY-DEEP-DIVE-2026-08-11 — RECLAIM program context, FDA RMAT designation, and the knee Phase 1 (NCT03672825) and hip (NCT0553132) registry entries