

TECHNICAL EVALUATION & CDMO FRAME

Encapsulated HEK-293 "Living Pharmacy

MADE technical evaluation and CDMO frame

PI	MAYO SITE	ON NUMBER	MODALITY	VERSION
Alexander Revzin, PhD	Rochester	806	Encapsulated allogeneic cell therapy	V01
PREPARED				
September 3, 2026				

Confidential — MADE Scientific and Mayo Clinic. Prepared under CDA. A technical assessment, not a proposal or an offer.

DEFY LIMITS. DELIVER RESULTS.

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	ARPA-H-funded encapsulated-cell "living pharmacy" for inflammatory bowel disease, built on HEK-293
Modality	Encapsulated allogeneic cell therapy — biologic plus device
Phase	Phase 1 / IND-enabling
Regulatory status	Pre-IND. An FDA INTERACT meeting is recorded as the next step — see §3
Starting material	HEK-293 cell line and expression construct. Bank-and-scale, not per-patient — one master cell bank supplies many doses
Drug substance	Expanded, harvested and concentrated engineered HEK-293 cells
Drug product	The assembled implant: cells sealed inside a semi-permeable capsule
Where MADE would manufacture	Princeton, NJ
MADE reference	Pre-proposal — no proposal issued
MADE technical fit	Direct. MADE already manufactures an allogeneic encapsulated cell therapy — see §13

This is a technical assessment, not a proposal.

2. Program understanding

An encapsulated cell therapy has three parts: an engineered cell line, a construct directing secretion of a therapeutic payload, and a semi-permeable capsule that admits nutrients and lets the payload out while containing the cells. Implanted locally, it delivers sustained local drug exposure without systemic dosing. The contemporary programs in this field are localized rather than systemic for a reason — delivering a cytokine into a body cavity, a joint or a lesion at concentrations that would be intolerable systemically is the proposition that revived the field.

Three things make the cell manufacturing here more straightforward than most cell therapy, and one thing makes it harder.

Allogeneic and immortalized means **bank-and-scale**. One master cell bank supplies many doses, with predictable facility utilization — the opposite of the autologous programs elsewhere in your portfolio. **HEK-293 is a bioprocessing workhorse and suspension-adaptable**: it runs directly on platforms we already operate. And **potency is more tractable here than in most cell therapy**, because the therapeutic entity is a defined secreted protein — see §7a.

What makes it harder is the capsule. HEK-293 is adenovirus-transformed and tumorigenic in immunocompromised models. For an implanted product the capsule is what stands between the cells and the patient, which makes capsule integrity a critical quality attribute rather than a packaging detail. Who makes it, to what specification, and how it is assembled and released is where this program actually gets hard. That sits in §5 and §8, and we would rather raise it at the start than discover it at month six.

3. Regulatory position and pathway

Current filing status	Pre-IND. Dr. Allickson's 18 August note records that this program has an INTERACT as its next step — an early FDA interaction rather than a later one
What that changes	It moves CMC content forward. The two things an agency in this modality concentrates on are cell-line provenance and characterization, and containment — so bank characterization and the capsule-integrity position become near-term needs rather than Stage 3 outputs. The target date and the CMC content Mayo needs in it are the first questions in §15
Designations held	Not established — see §15
Filing path	Combination product — biologic plus device. Device-side design controls apply alongside the biologic CMC package: design history file, risk management, and design confirmation sit next to the process. The capsule's performance is a design output to be demonstrated, not a process parameter to be controlled
What the CMC package must support	Phase 1. The January 2026 flexible-CMC position applies to the biologic side — before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected and specifications may be permissive. The device side is governed separately and its design-control expectations do not flex in the same way
What the agency will concentrate on	Containment. The safety argument for implanting a tumorigenic immortalized line rests on the capsule holding — what constitutes a breach, what test detects one, what sampling plan gives assurance across a batch of implants, what the acceptance criterion is, and what the retrieval or explant strategy is
Alongside that	Cell-line provenance and characterization; the adventitious-agent strategy including the E1 adenoviral sequences integrated in the line; tumorigenicity data; and biodistribution — whether any cells escape and what happens if they do
What a site change implies	The cell line's provenance and documentation transfer with it. If that documentation is inadequate, the remedy is not a comparability exercise — it is re-deriving a bank from a qualified source, which is a much larger piece of work
Applicable guidance	FDA CBER flexible-CMC announcement, 11 January 2026, on the biologic side; device design-control expectations on the other

For a team whose experience is biologic, the device side is the part most commonly underestimated, and an early conversation prevents the most rework. An INTERACT is the right place to have it.

4. Starting material

There is no per-patient collection in this program. The starting material is a cell line and a construct, received once, and everything downstream comes from a bank.

Source	HEK-293, engineered with an expression construct directing secretion of the therapeutic payload
What is not yet known	The payload itself. What the engineered cells secrete is the therapeutic entity , and without it the potency strategy, the release panel and the dose basis cannot be defined — see §15
Receipt	Cell line and construct receipt, establishing provenance. Whether an existing bank exists, and at what grade, is not established

Acceptance criteria	Provenance documented to a GMP-acceptable standard, with passage history. Many academic HEK-293 lines are not, and establishing provenance quality is the first thing to check before scoping anything else
Identity and custody	STR profiling and karyotype at the bank, with construct integrity and copy number by ddPCR and sequencing
Storage form	Cryopreserved bank vials in vapor-phase liquid nitrogen
Suspension or adherent today	Not established, and it decides the whole upstream design — see §5 and §15
On inadequate provenance	The equivalent of a failed collection. The remedy is re-deriving a bank from a qualified source rather than a comparability exercise, which is why the bank is the right first scope

5. Process flow

Unit operation	Your approach	MADE capability	Read
Cell line and construct receipt	Not established	Standard receipt with provenance established	Research-grade lineage documentation is a real problem, and it is checked first
Master cell bank	Not established — no bank grade confirmed	Bank manufacture with full characterization and safety testing	Characterization for an immortalized line is heavier than for a primary cell, and it is well preceded
Working cell bank	Not established	Bank manufacture	Sizing follows from cells per implant and implants per patient (§15)
Expansion	Suspension or adherent not established	Suspension runs directly on single-use platforms in service — see §6. An adherent route is available on hollow fiber	Suspension adaptation, where required, is a process development project with its own comparability question: adapted cells can differ in growth, in secretion rate and in construct stability
Harvest and concentration	Not established	Standard	Cell state at harvest drives secretion at the far end
Formulation into the encapsulation step	Not established	Standard	The interface between biologic and device manufacture. How long cells can be held between harvest and loading is an in-process control that has to be set
Encapsulation and device assembly	Not established — commonly manual at research scale	MADE can support the assembly step in a suitably classified environment. The capsule itself, its design controls and its integrity method belong to a device partner or to your team	The step that separates a working laboratory platform from a manufacturable process. Manual assembly of an implantable device at GMP requires an environment, a defined procedure, operator qualification and in-process controls that a research lab has not built
Device finishing, inspection and packaging	Not established	Environment classification to be agreed specifically	An open assembly step on an implantable product plausibly requires an ISO 5 environment

Unit operation	Your approach	MADE capability	Read
Release testing	Not established	See §7	Capsule integrity and secretion rate are both release attributes
Storage and shipping	Not established	See §9	The device and the cells have different stability constraints

On the device side we would be direct about our limits. MADE manufactures the biologic and can support the assembly step in a suitably classified environment. If there is no device partner today, we would rather help you scope that workstream than imply we build it.

6. Key equipment

Instrument	Your platform	MADE's installed position	Onboarding required
Suspension expansion, screening scale	Not established	Sartorius Ambr 15 × 1 in service at Princeton	None
Suspension expansion, vertical-wheel	Not established	PBS Biotech vertical-wheel × 6 in service at Princeton, at 3 MAG and 15 MAG	None
Stirred single-use bioreactor	Not established	Eppendorf BioFlo 320, to 40 L; Sartorius Biostat STR × 1 in service at East Norriton, 50 L single-use	None. Together these cover screening through 50 L
Rocking-bag expansion	Not established	Xuri / WAVE W25 × 21 in service at East Norriton	None
Adherent route, if the line is not suspension-adapted	Not established	Terumo Quantum Flex × 1 in service at Princeton, hollow fiber; Corning CellSTACK multi-layer vessels	None
Harvest concentration by tangential flow	Not established	Repligen KrosFlo KR2i systems are on site at East Norriton in warehouse storage rather than in service	Deployment state to be settled before a program is committed to it
Payload quantitation and bioassay readouts	Not established	SpectraMax M3 × 3 and Thermo plate readers × 2 in service; Varioskan Lux × 1 in service	Method development against a reference standard
Count and viability	Not established	NucleoCounter NC-200 × 7 in service at Princeton; Vi-CELL × 2 in service at East Norriton	None
Construct copy number and stability	Not established	Bio-Rad QX200 ddPCR × 5 in service; Thermo QuantStudio × 3 in service	Assay development per construct
Identity by flow	Not established	Beckman Coulter CytoFLEX 13-color × 4 in service at Princeton	None
Mycoplasma and endotoxin	Not established	BioFire × 3 and Endosafe × 7 in service across both sites	None

Instrument	Your platform	MADE's installed position	Onboarding required
Capsule integrity	Yours or a device partner's	Not a MADE capability and not implied as one — see §5	The method belongs with whoever owns the device

7. Analytical panel and release

There are two products in one here, and two panels.

Level	Attribute	Your method	MADE position	In house or outsourced
Cell bank	Identity and provenance	Not established	STR profiling, karyotype	Outsourced
Cell bank	Genetic stability, construct integrity and copy number	Not established	ddPCR, sequencing	In house on QX200 for copy number; sequencing outsourced
Cell bank	Adventitious agents, including the E1 adenoviral sequence strategy	Not established	In vitro and in vivo panels, PCR	Outsourced
Cell bank	Tumorigenicity	Not established	Assessment against the agency's expectation	Outsourced
Cell bank	Sterility, mycoplasma, endotoxin	Not established	Standard	In house
Drug product	Viable cell number per device	Not established	Automated count on a released device or a surrogate	In house
Drug product	Payload secretion rate	Not established	ELISA or bioassay on device-conditioned medium, against a reference standard	In house on the plate readers, once a reference standard exists
Drug product	Capsule integrity	Not established	The device-side method — the critical quality attribute of this product	Device partner or your team
Drug product	Sterility, endotoxin	Not established	Standard, on the assembled device	In house
Drug product	Construct stability over implant life	Not established	Stability program, not a release test — see §9	In house

Capsule integrity is where the analytical work concentrates and where the reference literature gives least help. It has to be defined operationally — what constitutes a breach, what test detects one, what sampling plan gives assurance across a batch of implants, and what the acceptance criterion is. It is a device-engineering question answered with device-engineering methods, and it belongs in the quality plan from the first engineering run rather than being retrofitted.

7a. Potency

Potency is more tractable here than in most cell therapy, not less. Because the therapeutic entity is a defined secreted protein, potency is a quantitation problem rather than a search: quantified payload secretion rate from the assembled drug product, measured on conditioned medium against a reference standard — not viability, not identity, not cell count. This modality inherits the biologics world's potency architecture, which is the easier one, and that is worth saying to anyone who assumes cell therapy potency is inherently hard.

Two things follow. **A bioassay should follow the immunoassay.** Quantifying the payload proves it is present; a cell-based response assay proves it is active. A protein that is immunoreactive and inactive is the failure mode an immunoassay alone cannot see, and it belongs at Phase 2. And **durability of secretion is the attribute the clinical mechanism actually depends on.** Construct silencing in immortalized lines over extended culture is a known phenomenon. A device that meets specification on day one and silences at week six has failed in a way no release test detects, so whether the construct is stable over the implant life is a characterization requirement, not an assumption.

8. Fill, finish and presentation

This is where the program gets hard, and it is a device question rather than a biologic one. The drug product is not a vial — it is an assembled implant, and the fill-finish equivalent is encapsulation, device assembly, inspection and packaging.

Container closure	The semi-permeable capsule itself. Material and design not established — see §15
Who makes it	Not established. If there is no device partner, that gap is larger than the cell manufacturing
Fill	Cells loaded into the capsule. Cells per implant, and implants per patient, are not established and they set bank size and the whole scale model
Assembly	Commonly manual at research scale. Whether it is manual or automated at GMP is not established, and it is the second question in §15
In-process controls	The controls on fill, the hold time between harvest and loading, and the inspection of each device are all to be defined
Assembly environment	Not established. An open device-assembly step on an implantable product plausibly requires an ISO 5 environment. MADE's suites run Grade B background with Grade A biological safety cabinets for open manipulations, and this step would need its classification agreed specifically rather than inherited
Labeling	Not established — see §15
Release of the assembled device	Viable cell number, secretion rate and capsule integrity — see §7

9. Stability, storage and shipping

The drug product is a device containing living cells, and the two components have different stability constraints.

Stability status	Not established — no program exists yet
What it must cover	Viable cell number per device, secretion rate, capsule integrity, and construct stability
Over what window	Shelf life and implant life are different clocks and both need data. The recurring failure modes in this field are durability problems rather than acute safety problems — fibrotic overgrowth limiting nutrient exchange and payload egress, loss of cell viability inside the capsule, and construct silencing reducing secretion — which is why implant-life data matters more here than shelf-life data
Storage condition	Not established. Whether the assembled device is shipped fresh, cryopreserved, or assembled near the point of use is a design decision with large downstream consequences, and it should be made explicitly rather than inherited from how the research group happened to do it
Cell bank storage	Vapor-phase liquid nitrogen
Shipper	Not established — see §15
Qualification status	Not established — see §15
Chain of custody, outbound leg	Not established — see §15

10. Comparability

Academic origin is the usual case in this modality, and the standard transfer-risk matrix places it at high risk with three to five bridging lots. This program carries a specific additional exposure on top of that: the cell line's provenance and documentation transfer with it, and if that documentation is inadequate the fix is not comparability — it is re-deriving a bank. **Establish provenance quality before scoping anything else.**

Change	Risk	Why
Cell line provenance or re-derivation	Highest	A different bank is a different product
Adherent to suspension adaptation	Highest	Growth, secretion rate and construct stability can all shift
Encapsulation method, materials or scale	Highest	The capsule is a critical quality attribute; a materials change is a device change
Construct or expression cassette	Highest	Changes the payload and its production
Bioreactor platform or scale	High	Standard bioprocess comparability
Formulation or hold time before encapsulation	Medium-High	Cell state at loading drives secretion

The analytical bridge is unusually clean here. Because the therapeutic entity is a defined secreted protein, secretion rate against a reference standard carries the comparability argument, with viable cell number per device making it interpretable and capsule integrity read alongside. A suspension adaptation, if one is required, is bridged on growth, secretion rate and construct stability together — not on growth alone, which is the reading that misses the failure.

11. Technology transfer approach

Stage	What happens	Where the gate sits
Stage 0 — technical assessment	This document and the questions in §15. Expect provenance, the encapsulation step and the device partnership question to be the three largest open items	The four questions at the head of §15
Stage 1 — GMP master and working cell bank	Bank establishment with full characterization and safety testing, including the E1 adenoviral sequence strategy and tumorigenicity. Discrete, bounded and fast; it de-risks everything downstream and requires no agreement on structure, facility or long-term commitment	Bank release and characterization data reviewed jointly
Stage 2 — process definition and suspension adaptation	Where required, with secretion rate tracked as the process readout rather than as an endpoint	Suspension adaptation bridged on growth, secretion and construct stability
Stage 3 — engineering run through encapsulation	Including the device assembly step at the intended environment classification, producing the first real capsule-integrity dataset	The capsule-integrity method and its acceptance criterion agreed before the run, not after
Stage 4 — comparability and GMP manufacture	With the combination-product path settled and device-side design controls in place	A stage-gate readiness assessment before GMP activity begins

Start with the bank. It is discrete, it needs no structural decision, and it is the same shape of scope your institution already understands from cell-bank work elsewhere in the portfolio. Characterization for an immortalized line is heavier than for a primary cell and the scope is well established: identity and provenance, purity, viability, sterility, mycoplasma, endotoxin, comprehensive adventitious agent testing, karyotype and genetic stability, and tumorigenicity assessment — plus the E1 strategy.

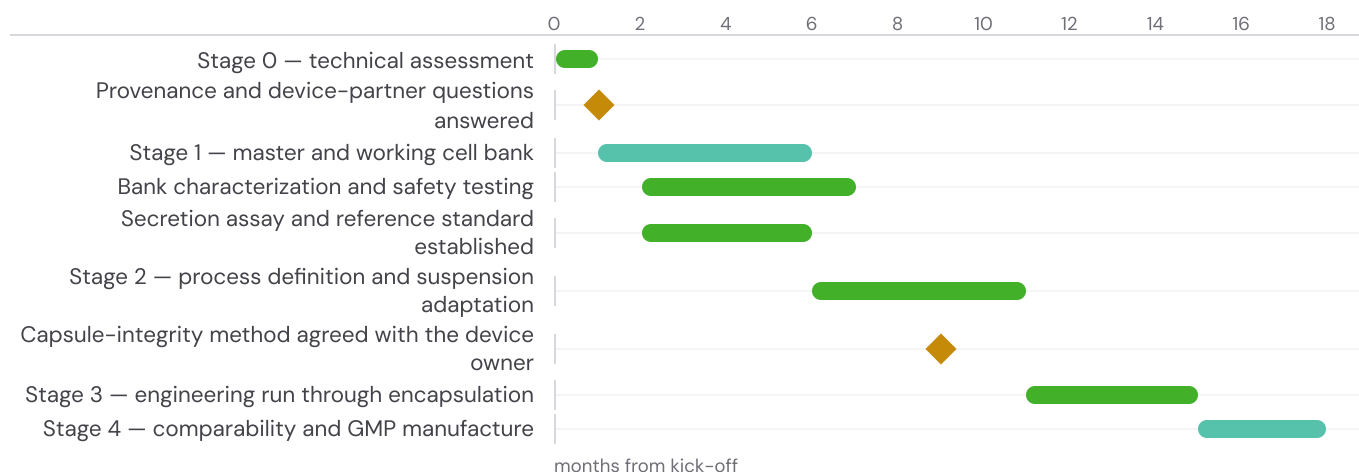
How this becomes a proposal. A MADE proposal presents this plan as numbered work orders grouped into milestones — process establishment and feasibility, process and analytical development, GMP readiness, and GMP manufacture — with each work order carrying its own deliverables, assumptions and exclusions, 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.

12. Indicative timeline

Stage	Duration
Stage 0 — technical assessment	2–4 weeks
Stage 1 — master and working cell bank with characterization	Months, rather than the 12–18 months a full custom cell therapy process takes [industry range]
Stage 2 — process definition and suspension adaptation, where required	Not established until the adherent-or-suspension question is answered

Stage	Duration
Stage 3 — engineering run through encapsulation	Not established until encapsulation ownership and automation are settled
Stage 4 — comparability and GMP manufacture	Follows the combination-product path being settled

Two things set the real clock. **Where funding runs on milestones, the milestone schedule is the timeline**, and aligning the first scope of work to the next milestone is usually the fastest route to a signed project — which is why the next funder milestone and its date is a question in §15. And **an INTERACT as next step pulls CMC content forward**: the bank characterization data and the capsule-integrity position are the two things most likely to be asked for, and both sit in Stage 1 and Stage 3 below. Until the INTERACT target date is fixed, the sequence below is drawn from kick-off rather than against it.



The bars show sequence and dependency, not committed dates. Stage 1 is the only one of them that can be scoped today.

13. MADE experience that supports this

Direct precedent, publicly on record. In July 2025 MADE announced a manufacturing partnership with Sentinel BioTherapeutics for SENT-001 — an allogeneic encapsulated cell therapy using genetically engineered ARPE-19 cells to deliver native human IL-2 to the peritoneal or pleural cavities, evaluated under NCT05538624. MADE established the GMP master cell bank and supports process optimization and clinical GMP drug product manufacture as an off-the-shelf product. The structural match to a HEK-293-based encapsulated program is close: same product architecture, same bank-and-scale shape, same combination-product path. An implanted, encapsulated allogeneic cell product is not an adjacent capability for us; it is a program already in the building.

Expansion platforms. Publicly named: Corning CellSTACK, Eppendorf BioFlo 320, Sartorius Biostat STR, Terumo BCT Quantum Flex, PBS Biotech vertical-wheel, with single-use bioreactor technology transfer advancing toward client readiness. For a HEK-293 suspension process this covers screening through 50 L, with an adherent route available if the line has not been suspension-adapted.

Analytical bench. Multi-mode plate reading for payload quantitation and bioassay readouts; NucleoCounter NC-200 and Vi-CELL for count and viability; Bio-Rad QX200 ddPCR and Thermo QuantStudio for construct copy number and stability; Beckman Coulter CytoFLEX for identity; NanoDrop for nucleic acid quantitation. Tumorigenicity, adventitious agent panels, karyotype and identity profiling are outsourced, which is standard for cell-bank characterization.

Quality. MADE's quality and regulatory leadership carries collective experience from prior organizations across cell therapy quality systems, aseptic manufacture and method qualification, and 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.

Facilities. Princeton, NJ and East Norriton, PA. Grade B background with Grade A biological safety cabinets for open manipulations, and Grade B / Closed System for closed steps.

14. Guidance and suggestions

Start with the bank, and start it now. It is discrete, it de-risks everything downstream, it requires no decision on facility or structure, and — with an INTERACT ahead — bank characterization data is among the most likely things the agency will want to see. It is the one piece of this program that can begin without any wider decision being made.

Check provenance before anything else. Where the line came from, its passage history, and whether the lineage is documented to a GMP-acceptable standard. The remedy for inadequate documentation is re-deriving a bank, not a comparability exercise, and that is a difference measured in months.

Settle the device workstream early. Who makes the capsule, to what specification, under whose design controls, and how it is assembled and released. If there is no device partner today, scoping that workstream is more useful to you than any capability claim we could make about it.

Treat implant-life durability as a characterization requirement, not an assumption. Construct silencing over extended culture is the recurring failure mode in this field, and it is invisible to a release test.

15. Open questions

We would ask these four first.

1. **The INTERACT** — what is the target date, and what CMC content do you need in it? That question sets the sequencing of everything else.

1. **What does the payload secrete**, and is the construct stable over the implant life — is there data, or an assumption?

1. **Who makes the capsule, and is there a device partner?** Who performs encapsulation today, at what scale, and is it manual?

1. **Suspension or adherent?** If adherent, is suspension adaptation planned — that decides the

bioreactor path.

Scale and bank. Cells per implant and implants per patient, which sets bank size and the whole scale model. Cell-line provenance and passage history, and whether an existing bank exists and at what grade.

Regulatory. Are any designations held or planned? Has the combination-product path been confirmed, and who holds device-side design controls? What tumorigenicity and biodistribution package do the funder and the agency expect?

Presentation and logistics. What is the intended container closure and capsule material? What labeling applies to an implanted combination product? Is the assembled device shipped fresh, cryopreserved, or assembled near the point of use — and which shipper and lane would carry it?

Funding. What is the next funder milestone and its date? Where funding runs on milestones, that schedule is the real timeline.

16. Suggested next step

A technical call covering the four questions above, with the INTERACT first. If the answers point where we expect, a scoped cell-bank proposal could follow within days rather than weeks — and that is a project that can start without any wider decision being made.