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From Agglomeration to Release: A Stage-Appropriate MSC Process that Scaled Cleanly

When mesenchymal stem cells (MSCs) behave, they are remarkably manufacturable. When they do not, the challenges show up in the same places every time: inconsistent expansion, agglomeration at harvest, and a drug product (DP) step that becomes the silent source of release delays.

This case study follows a common pattern we see in MSC programs: a process that works at a small scale, then starts to drift as you increase lot size or throughput. The goal was not to invent a "forever" commercial process on day one. The objective was to implement stage-appropriate improvements that stabilized yield and release performance immediately, while preserving a clear and rational path to scale.

The Situation

The program was operating on an accelerated early clinical timeline using a standard MSC workflow built around initiation and two-dimensional expansion cycles. While the process remained functional, variability was increasing and downstream operations were absorbing the impact.

Observed Challenges

- Drift in cell growth and harvest timing
- Increased agglomeration around harvest and wash
- Release delays driven by DP appearance and handling

These were symptoms, not root causes. We approached the problem as an engineering exercise rather than a troubleshooting exercise.

Step 1: Make the Root Cause Discussable

The team conducted a structured fishbone (Ishikawa) root-cause analysis and aligned on the single most urgent failure mode to address first.

This consistently narrowed focus to two areas:

- Upstream growth control, including media strategy and cell density management
- Downstream stress and agglomeration during harvest and wash

Step 2: Stabilize Growth Using Measurable Signals

Upstream operations shifted from schedule-based feeding to a defined media exchange strategy anchored in observed cell growth behavior.

In-process metabolite monitoring was introduced to provide earlier, objective indicators of metabolic stress and growth drift.

This matters because MSCs often appear acceptable until performance degrades rapidly. Metabolite trends enable earlier and more repeatable decision-making.

Step 3: Address Agglomeration at the Unit Operation Where It Forms
Agglomeration directly affects fill accuracy, viability, and post-thaw performance. The downstream solution combined:

- In-line filtration to reduce clumping without excessive mechanical stress
- Improved process flow and labor efficiency to shorten harvest time
- Automated cell washing to reduce operator-dependent shear variability and improve pellet consistency, with a clear path toward large-scale automation as throughput grows

This is where experienced infrastructure accelerates execution. Made Scientific supports MSC programs with established platforms for harvest, wash, formulation, and DP preparation, including systems such as LOVO® and Rotea™, enabling automation without custom engineering from scratch.

Step 4: Reduce Release Friction with a Defined DP Workflow
Release delays are often driven by small ambiguities that compound at scale. The updated process incorporated:

- Defined visual inspection criteria to reduce subjective release decisions
- A DP fill approach aligned with aseptic processing realities, treating fill & finish as integrated part of the manufacturing operation rather than a downstream afterthought

The Result (or Outcome)
The final output was a platform direction, not a one-off fix: an MSC process that improved yield consistency, reduced agglomeration, and improved the probability of on-time release, while remaining realistic for the stage of development.

The core lesson was simple: tightening the few unit operations that drive most variability creates disproportionate gains in robustness and scalability.

Ready to discuss this topic further with our Subject Matter Experts? Let's talk.

About Made Scientific

Made Scientific is a leading U.S.-based cell therapy contract development and manufacturing organization (CDMO) specializing in the development, manufacturing, and release of autologous and allogeneic cell therapy products for clinical- and commercial-supply. Operating from two state-of-the-art manufacturing facilities in New Jersey, Made Scientific combines the agility and entrepreneurial spirit of a specialist CDMO with the global expertise and resources of GC Corporation of South Korea, a global leader in the pharmaceutical and biotechnology sectors. For more information, visit www.madescientific.com.

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