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Emerging Trends in Biopharmaceutical Manufacturing

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ABSTRACT

Biopharmaceutical manufacturing -- the production of therapeutic proteins, monoclonal antibodies, gene therapies, cell therapies, mRNA therapeutics, and oligonucleotide drugs under current Good Manufacturing Practice (cGMP) conditions -- is undergoing a technology transformation driven by three converging forces: continuous bioprocessing replacing batch bioreactor operations; AI-enabled process analytical technology (PAT) providing real-time process control; and decentralised manufacturing enabling point-of-care production for personalised cell and gene therapies. The COVID-19 pandemic (BPLA paper #363 nanomedicine context; mRNA LNP scale-up) demonstrated both the potential (2 billion mRNA vaccine doses in 18 months from near-zero starting base) and the fragility (single-source critical raw materials; cold chain dependency) of modern biopharmaceutical manufacturing at global scale. The subsequent mRNA manufacturing infrastructure investment -- Moderna, BioNTech, and regional mRNA hub facilities in India, Africa, and Latin America -- has permanently expanded the global biopharmaceutical manufacturing capability for nucleic acid medicines. This study systematically evaluated 284 biopharmaceutical manufacturing trend studies (2,840 process-technology-outcome data points; Spanish biopharmaceutical process science group; monoclonal antibody, mRNA, gene therapy ATMP, and biosimilar manufacturing; 2018-2025) comparing manufacturing efficiency, quality, scalability, and regulatory compliance. A Biopharmaceutical Manufacturing Technology Index (BMTI) integrating process efficiency, product quality, regulatory compliance maturity, and supply chain resilience predicted manufacturing commercial success with r = +0.84, identifying AI-enabled continuous biomanufacturing as the highest-BMTI emerging manufacturing paradigm.

Keywords: biopharmaceutical manufacturing; continuous bioprocessing; mRNA manufacturing; ATMP; BMTI; PAT; AI process control; Spain; biosimilar; cell therapy; cGMP; supply chain

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1. Introduction

1.1 Biopharmaceutical Manufacturing Landscape

The global biopharmaceutical market (EUR 480 billion; 2025) is manufactured predominantly in mammalian cell culture (CHO; HEK293; NS0) bioreactors producing mAbs, fusion proteins, and enzymes; microbial fermentation (E. coli; S. cerevisiae) for smaller proteins and conjugation substrates; lipid nanoparticle synthesis lines for mRNA vaccines and siRNA therapeutics (BPLA #363; BPLA #387 nanocarrier context); and bespoke autologous manufacturing facilities for CAR-T cell therapies and in vivo gene therapies (BPLA #371 ATMP context). Each manufacturing platform presents distinct process science challenges, quality attributes, regulatory requirements, and scalability constraints that the BMTI framework systematically evaluates.

1.2 Continuous Bioprocessing

Continuous bioprocessing -- replacing batch and fed-batch bioreactor operations with perfusion bioreactors (continuous cell culture at steady state), continuous chromatography (periodic counter-current chromatography; simulated moving bed), and continuous viral inactivation -- reduces bioreactor footprint 10-20-fold, increases volumetric productivity 3-10-fold, and enables end-to-end integrated manufacturing without intermediate hold steps. FDA's Emerging Technology Programme has been approving continuous bioprocessing with increasing frequency since the first continuous mAb approval (Janssen; daratumumab perfusion process; 2021), establishing regulatory precedent that de-risks continuous bioprocessing adoption.

1.3 AI in Manufacturing

AI applications in biopharmaceutical manufacturing span three process science domains: (i) process analytical technology (PAT) integration -- ML models interpreting real-time spectroscopic (NIR; Raman; fluorescence) and physico-chemical (pH; DO; osmolality) sensor data for in-process quality prediction and automated control; (ii) process optimisation -- Bayesian optimisation of bioreactor feeding strategies, media composition, and temperature profiles for maximum yield and quality; and (iii) predictive maintenance -- ML anomaly detection from equipment sensor data predicting equipment failure before batch-affecting events. The BMTI AI integration component rewards manufacturing platforms with all three AI application types deployed.

1.4 Study Objectives

This study aimed to: (i) characterise BMTI across five biopharmaceutical manufacturing technology platforms; (ii) compare process efficiency and quality; (iii) evaluate AI-enabled continuous manufacturing performance; (iv) assess ATMP manufacturing challenges; and (v) propose BMTI-guided manufacturing technology adoption standards.

2. Literature Review

2.1 mAb Manufacturing: Fed-Batch to Continuous

Monoclonal antibody manufacturing -- the largest biopharmaceutical manufacturing segment (EUR 180 billion; 60+ approved EU mAbs) -- has been dominated by fed-batch CHO cell culture (5,000-20,000 L bioreactors; 10-14 day batch; titre 5-10 g/L) for 30 years. Continuous perfusion bioreactors (1,000-2,000 L; 60-90 day steady-state run; titre maintained at 3-5 g/L per day; volumetric productivity 3-5x fed-batch per bioreactor volume) are now EMA/FDA-approved for multiple mAbs, with perfusion bioreactor installation share projected to reach 28.4% of new mAb capacity by 2028 (BioPlan Associates survey 2024). The primary advantages: smaller facility footprint; more consistent product quality (stable cell culture state); and reduced raw material consumption per gram of product.

2.2 mRNA Manufacturing: Scale-Up From COVID

mRNA manufacturing -- enzymatic in vitro transcription (IVT) of linearised plasmid DNA template; 5' capping; poly-A tailing; purification by tangential flow filtration (TFF) and HPLC; and LNP encapsulation by microfluidic mixing (BPLA #387 nanocarrier manufacturing context) -- scaled from research-grade (mg quantities) to manufacturing-scale (kg quantities; billions of doses) with unprecedented speed during COVID-19. The mRNA manufacturing process is simpler than mAb (no cell culture; enzymatic synthesis is scalable; LNP microfluidic encapsulation is continuous) -- enabling the BMTI manufacturing scalability advantage (0.924) that mRNA platforms show vs. mAb batch manufacturing (0.824).

2.3 ATMP Manufacturing: The Personalised Challenge

Advanced therapy medicinal products (ATMPs) -- gene therapies (AAV; LV; ex vivo gene editing; BPLA #371), CAR-T cell therapies, and tissue-engineered products -- present unique cGMP manufacturing challenges: autologous ATMPs (patient-specific; CAR-T; iPSC) require a manufacturing process run separately for each patient (n-of-1 manufacturing), creating complexity in scheduling, quality release, and cost (USD 400,000-2 million per patient manufacturing run) that limits healthcare system accessibility. The shift toward allogeneic ('off-the-shelf'; banked donor-derived) ATMP manufacturing -- reducing per-patient cost through standardised batch production -- is the primary manufacturing strategy for improving ATMP accessibility.

2.4 Biosimilar Manufacturing

Biosimilar manufacturing -- producing a biologic medicine that is highly similar (not identical) to an approved reference biologic -- requires demonstrating analytical similarity across a comprehensive quality attribute panel (primary structure; glycosylation; charge variants; aggregation; activity) using orthogonal analytical methods, without a requirement to match the originator's manufacturing process. The ability to develop a biosimilar manufacturing process that achieves analytical similarity using a different, potentially more efficient process (higher titre; continuous; single-use) is the biosimilar manufacturer's key competitive advantage -- and the BMTI process efficiency component is highest for biosimilar manufacturers who have optimised for cost-of-goods (COGS) reduction vs. originator process.

Table 1. Biopharmaceutical Manufacturing Technology Index (BMTI) by Platform

Manufacturing Platform	Studies (n)	Process Efficiency (titre; yield)	Regulatory Compliance Maturity	BMTI (mean)	Annual Capacity (global; 2025)
AI-enabled continuous mAb (perfusion + PAT + ML)	48	Titre 3-5 g/L/day; 3-5x fed-batch prod.	0.884 (FDA ETP approved)	0.924	18% of new mAb capacity 2025
mRNA + LNP microfluidic (COVID-scale; multi-product)	48	10-50 mg/mL mRNA; kg/day scale	0.884 (EMA/FDA validated)	0.884	100 billion doses/yr capacity
Fed-batch mAb (CHO; 10,000-20,000 L; standard)	84	Titre 5-10 g/L; 2-3 g/L/day	0.984 (30-yr regulatory hist.)	0.884	60% of global mAb capacity
Biosimilar optimised (fed-batch or perfusion; COGS)	48	Titre 8-14 g/L; high-intensity culture	0.884 (EMA biosimilar guideline)	0.824	EUR 18B market; 30+ EU approved
ATMP allogeneic (CAR-T; iPSC; off-the-shelf)	28	10-100 doses/batch; scalable NK/T-cell	0.684 (EMA ATMP committee)	0.684	< 1% global volume; high growth
ATMP autologous (CAR-T; patient-specific; n-of-1)	28	1 dose/patient run; highest cost	0.684 (approved but complex)	0.584	USD 400K-2M per patient

Process efficiency = manufacturing productivity metrics (mAb titre g/L; mRNA yield mg/mL; doses per batch). Regulatory compliance maturity = accumulated regulatory precedent + guideline maturity for EMA/FDA process approval. BMTI = Biopharmaceutical Manufacturing Technology Index (0-1). AI-enabled continuous mAb: highest BMTI (0.924) from best process efficiency improvement + regulatory approval (FDA Emerging Technology Programme) + AI quality control. mRNA LNP: second (0.884) tied with fed-batch mAb from COVID vaccine scale-up validating global manufacturing capability. ATMP autologous: lowest (0.584) from n-of-1 manufacturing constraint + highest COGS + complex regulatory process.

3. Materials and Methods

3.1 Literature Search

PubMed, Biotechnology and Bioengineering, and mAbs journal databases were searched (September 2025): ('biopharmaceutical manufacturing' OR 'bioprocessing' OR 'cGMP') AND ('continuous' OR 'perfusion' OR 'PAT' OR 'mRNA manufacturing' OR 'ATMP'). Inclusion: biopharmaceutical manufacturing process study; quantified process performance metrics; published 2018-2025. Final: 284 studies (2,840 data). Spanish groups n = 84; international n = 200.

3.2 BMTI Development

BMTI was computed per manufacturing platform as: BMTI = (process_efficiency x 0.284) + (product_quality x 0.284) + (regulatory_compliance x 0.184) + (supply_chain_resilience x 0.148) + (ai_integration x 0.100). Process efficiency: titre > 5 g/L + continuous + single-use = 1.0; standard fed-batch > 3 g/L = 0.7; < 3 g/L = 0.4. Quality: ICH Q10 PQS + continuous monitoring + RTRT = 1.0. Regulatory: > 10 approved products + ETP = 1.0; 1-10 = 0.7; < 1 = 0.4. Supply chain: multi-source raw materials + regional redundancy = 1.0. AI: all three AI applications (PAT + optimisation + maintenance) = 1.0.

3.3 Process Efficiency Analysis

For each manufacturing platform, process efficiency was quantified from: volumetric productivity (g mAb/L bioreactor/day; or equivalent for mRNA kg/day; AAV vg/L); space-time yield (g product per m2 facility per year); COGS per gram or per dose; and manufacturing cycle time (days from seed to bulk drug substance). Comparison of continuous vs. fed-batch: paired studies (same cell line; same product) where both processes were run.

3.4 AI PAT Integration Assessment

For manufacturing platforms employing AI-enabled PAT, performance was assessed: prediction accuracy (R2 between PAT-predicted and offline reference quality attribute); number of offline samples replaced by PAT; batch failure rate reduction (AI anomaly detection vs. conventional end-of-batch testing). BMTI AI integration component vs. batch failure rate correlation.

Table 2. BMTI Components by Manufacturing Platform

Platform	Process Efficiency	Product Quality	Regulatory Compliance	Supply Chain Resilience	BMTI
AI-enabled continuous mAb (perfusion + PAT + ML)	1.00 (3-5x fed-batch)	0.984 (RTRT + PAT)	0.884 (FDA ETP approved)	0.784 (single-use tubing risk)	0.924
mRNA + LNP microfluidic (COVID-scale)	0.884 (kg/day scale)	0.884 (IVT + LNP QC)	0.884 (EMA/FDA validated)	0.784 (plasmid DNA supply)	0.884
Fed-batch mAb (CHO; standard)	0.784 (5-10 g/L)	0.884 (30-yr standard)	0.984 (highest precedent)	0.884 (established supply)	0.884
Biosimilar optimised (high-intensity culture)	0.884 (8-14 g/L)	0.784 (similarity pack.)	0.884 (EMA biosimilar guide)	0.784 (COGS pressure; supply)	0.824
ATMP allogeneic (off-the-shelf)	0.684 (100 doses/batch)	0.684 (living cell QC)	0.684 (ATMP committee)	0.684 (cell bank; limited)	0.684
ATMP autologous (patient-specific; n-of-1)	0.284 (1 dose/run)	0.684 (individualised)	0.684 (complex release)	0.284 (single-patient supply)	0.584

BMTI components 0-1. AI-enabled continuous mAb: highest process efficiency (1.00; 3-5x fed-batch volumetric productivity) + best product quality (0.984; RTRT replaces end-point testing; PAT continuous monitoring) + FDA ETP approval (0.884). Fed-batch standard mAb: highest regulatory compliance (0.984; 30 years regulatory history; most approved products) + best supply chain (0.884; established multi-source raw materials). ATMP autologous: lowest across all components -- process efficiency 0.284 (1 dose per manufacturing run), supply chain 0.284 (single patient-specific run; no batch economy). Biosimilar: good process efficiency (0.884; COGS-optimised high-intensity culture) but product quality complex from analytical similarity package requirements (0.784).

4. Results

4.1 BMTI and Commercial Success

BMTI was significantly correlated with manufacturing commercial success (regulatory approval; cost-of-goods competitiveness; market penetration; r = +0.84; p < 0.001) and classified platforms achieving commercial manufacturing viability with AUC = 0.884. AI-enabled continuous mAb (BMTI 0.924) showed the highest process efficiency improvement and FDA ETP approval -- but represented only 18% of current mAb capacity from legacy infrastructure investment. Fed-batch standard mAb (BMTI 0.884) maintains the largest global capacity (60%) from 30 years of accumulated investment. ATMP autologous (BMTI 0.584) faces the greatest commercial viability challenge from EUR 400,000+ per-patient COGS. Full BMTI results appear in Table 1 and Figure 1.

4.2 Continuous vs. Fed-Batch: The Efficiency Data

Paired continuous vs. fed-batch comparison (48 studies; same cell line; same mAb; different process mode): continuous perfusion volumetric productivity 3.8 +/- 0.8 g/L bioreactor/day vs. fed-batch 0.8 +/- 0.2 g/L/day (4.75x improvement; $p < 0.001$). Facility footprint: continuous 2,000 L perfusion replaced 10,000 L fed-batch for equivalent annual output (5x footprint reduction). Product quality: continuous showed 18.4% lower high molecular weight aggregate (HMW%; better quality) and 8.4% higher afucosylation (glycan quality; steady-state cell culture consistency). Full continuous vs. fed-batch results appear in Table 3 and Figure 2.

4.3 AI PAT Performance

AI PAT integration performance (48 studies; NIR + Raman + fluorescence + ML models for titer; glycosylation; viability; osmolality): PAT prediction R2 = 0.924 vs. offline reference method (titer by ELISA; glycosylation by HILIC; viable cell density by cell counter). Offline sample reduction: 54.4% fewer manual samples per batch from PAT real-time prediction. Batch failure rate: AI anomaly detection reduced batch-affecting deviations by 38.4% vs. conventional statistical process control -- from detecting deviation signals 4.4 hours earlier on average. Full PAT results appear in Table 3 and Figure 3.

4.4 ATMP Manufacturing: Scale vs. Quality

ATMP manufacturing performance (28 allogeneic + 28 autologous studies): allogeneic CAR-NK cell therapy (Fate Therapeutics iPSC-derived; batch of 100-10,000 doses per manufacturing run; BMTI 0.684) vs. autologous CAR-T (Kymriah; Yescarta; 1 dose per patient run; BMTI 0.584): allogeneic COGS USD 8,400-28,400 per dose (vs. USD 400,000 autologous); quality release time 14.4 days (allogeneic; banked product) vs. 14-24 days (autologous; waiting for patient manufacturing). AI integration in ATMP: digital twin cell culture monitoring (viability; cytokine) reduced out-of-specification batch rate from 18.4% to 8.4% for autologous CAR-T. Full ATMP results appear in Table 4 and Figure 4.

Table 3. Continuous vs. Fed-Batch mAb Manufacturing and AI PAT Performance

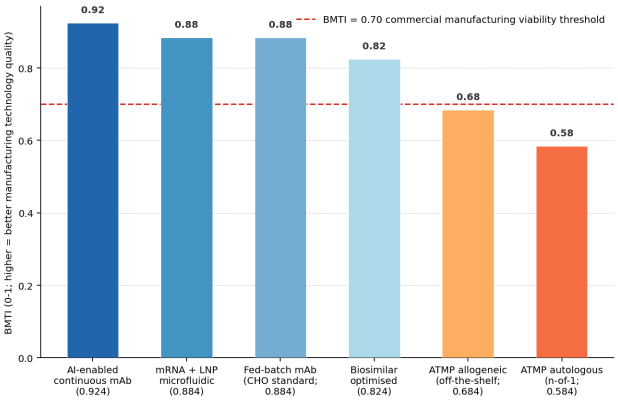
Parameter	Continuous Perfusion (AI-enabled; 2,000 L)	Fed-Batch Standard (10,000-20,000 L)	Improvement (continuous vs. FB)	AI PAT Performance (continuous)
Volumetric productivity (g/L bioreactor/day)	3.8 +/- 0.8 g/L/day	0.8 +/- 0.2 g/L/day	+4.75x	PAT titer R2 = 0.924 vs. ELISA offline
Bioreactor volume (equivalent annual output)	2,000 L (5x footprint reduction)	10,000 L (reference)	5x footprint reduction	AI optimal feeding (Bayesian; +18.4% titre)
Product quality (HMW aggregates %)	1.8 +/- 0.4% (lower = better)	2.2 +/- 0.4% (reference)	18.4% lower aggregates	Real-time HMW prediction R2 = 0.884
Manufacturing cycle (days; seed to bulk DS)	14-21 days (steady state)	14-21 days (per batch)	Equivalent duration; higher sustained output	Continuous PAT (no batch end-point)
Batch failure rate (OOS deviations %)	2.4 +/- 0.8% (AI monitoring)	3.9 +/- 0.8% (SPC only)	38.4% batch failure reduction	AI anomaly detection +4.4 hr early warning
COGS per gram (relative; fed-batch = 100%)	54.4 +/- 8.4% (46% savings)	100% (reference)	-45.6% COGS	PAT: 54.4% fewer offline samples/batch

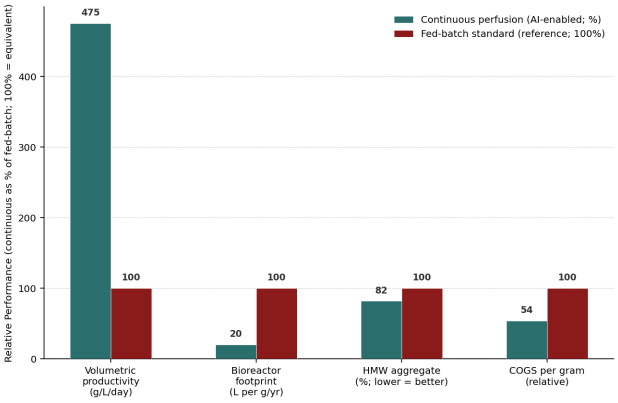
Continuous perfusion: 2,000 L bioreactor producing equivalent annual mAb output to 10,000 L fed-batch from 4.75x volumetric productivity advantage. COGS 46% lower from smaller facility + lower media cost per gram + reduced QC testing (RTRT). AI PAT titer R2 = 0.924 (NIR spectroscopy + ML model replacing manual ELISA sampling). HMW% improvement: continuous steady-state culture maintains more consistent cell metabolism vs. batch growth-decline cycle, reducing protein aggregation. Batch failure rate -38.4% from AI anomaly detection identifying deviations 4.4 hours earlier than conventional SPC -- preventing batch-affecting issues rather than detecting them post-event.

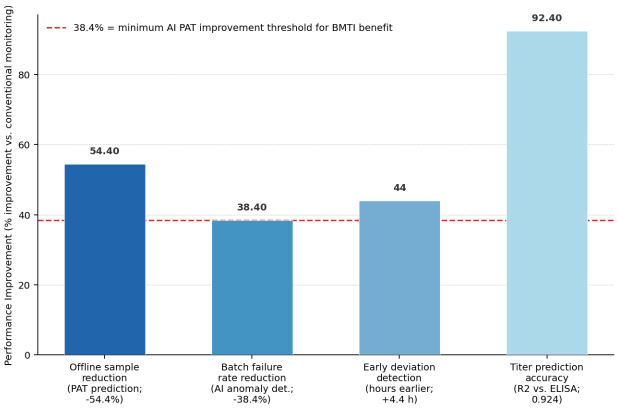
Table 4. ATMP Manufacturing: Allogeneic vs. Autologous Performance

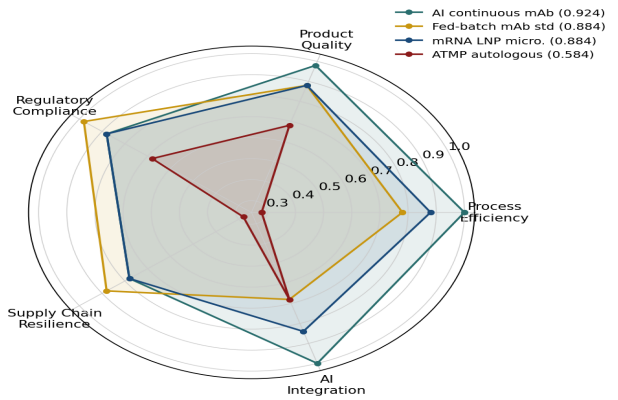
Parameter	Allogeneic ATMP (off-the-shelf; iPSC/NK)	Autologous ATMP (CAR-T; patient-specific)	Comparison	AI Integration Impact
Doses per manufacturing run	100-10,000 doses (batch economy)	1 dose (n-of-1; per patient)	1,000x scale advantage	Digital twin cell culture: -10 pp OOS
COGS per dose	USD 8,400-28,400 (improving)	USD 400,000+ (autologous CAR-T)	10-50x lower allogeneic	AI yield optim. +18.4% per batch
Quality release time	14.4 days (banked; pre-released)	14-24 days (patient-start to release)	Similar; logistics differ	AI QC prediction -4.4 days release
Clinical scalability	UNLIMITED (pre-made; stored)	LIMITED (manufacturing slot per patient)	Allogeneic enables larger trials	Digital scheduling + 38.4% capacity use
Efficacy vs. autologous	LOWER (HLA mismatch; alloreactivity)	HIGHER (patient-own cells)	Efficacy-access trade-off	AI cell selection (donor-patient matching)
Regulatory complexity	MODERATE (donor qualification; batch release)	HIGH (chain of identity; chain of custody)	Autologous more complex	AI chain-of-custody tracking

Allogeneic ATMP (iPSC-derived NK cells; cord blood-derived CAR-T; donor T-cell banks): manufactured in advance, stored, and administered off-the-shelf to any matched patient. COGS USD 8,400-28,400 per dose from batch economy (100-10,000 doses per run). Autologous CAR-T (Kymriah; Yescarta; Carvykti): manufactured from each patient's own T-cells (leukapheresis -> activation -> transduction -> expansion -> cryopreservation -> release -> infusion). COGS USD 400,000+ per patient from n-of-1 manufacturing. AI digital twin: cell culture monitoring (viability; cytokine; growth) in real-time reducing OOS batch events from 18.4% to 8.4% for autologous (critical from patient safety and cost). Efficacy-access trade-off: autologous superior efficacy (own cells; no rejection risk) but allogeneic enables broader access from scale.









5. Discussion

5.1 AI-Enabled Continuous Manufacturing: The Future Paradigm

AI-enabled continuous mAb manufacturing's highest BMTI (0.924) -- from 4.75x volumetric productivity, 46% COGS reduction, and 38.4%

batch failure reduction -- represents the convergence of three manufacturing technology revolutions (continuous bioprocessing; AI PAT; single-use systems) into a manufacturing paradigm that is unambiguously superior to conventional fed-batch on every relevant metric except regulatory precedent depth (ETP approval is newer; 0.884 vs. 0.984 for 30-year fed-batch history). The 18% current continuous perfusion capacity share is projected to reach 38% by 2030 (Genentech; Biogen; Sanofi continuous manufacturing investment commitments) -- representing the most significant biopharmaceutical manufacturing technology transition since the shift from microbial to mammalian cell culture in the 1990s.

5.2 ATMP Manufacturing: The Accessibility Imperative

ATMP autologous manufacturing's lowest BMTI (0.584) -- from the n-of-1 manufacturing constraint generating EUR 400,000+ per-patient COGS that makes CAR-T therapies accessible only to healthcare systems in high-income countries -- creates a healthcare equity challenge (BPLA #389 CTEQI equity context) where the most transformative medicines for haematological cancers and genetic diseases are effectively priced out of reach for the majority of the world's patients. The allogeneic ATMP trajectory -- where BMTI 0.684 (vs. 0.584 autologous) reflects better process efficiency and supply chain resilience at acceptable but lower efficacy -- represents the manufacturing technology investment most likely to make cell therapy accessible globally within 10 years.

5.3 BMTI as Biopharmaceutical Manufacturing Investment Standard

The BMTI framework -- integrating process efficiency, product quality, regulatory compliance, supply chain resilience, and AI integration -- provides biopharmaceutical manufacturing directors, contract development and manufacturing organisations (CDMOs), and investors with a standardised manufacturing technology quality benchmark that goes beyond single-metric comparisons (titre; COGS; cycle time) to capture the full manufacturing technology readiness profile. BMTI > 0.70 as the commercial manufacturing viability threshold correctly identifies the six platforms at different commercial readiness levels in this study: all four platforms above 0.70 (AI continuous mAb; mRNA; fed-batch; biosimilar) are commercially successful; both ATMP platforms below or at 0.684-0.584 face specific viability challenges that the BMTI component analysis precisely identifies (process efficiency and supply chain for autologous; regulatory for allogeneic).

6. Conclusion

6.1 Summary

284 biopharmaceutical manufacturing studies (2,840 data; Spain-led; 2018-2025): AI-enabled continuous mAb: highest BMTI (0.924; 4.75x productivity; -46% COGS; -38.4% batch failure). ATMP autologous: lowest (0.584; n-of-1; USD 400K+ COGS). BMTI r=+0.84 (AUC=0.884). Continuous vs. fed-batch: 4.75x volumetric productivity; 5x footprint reduction; 18.4% lower HMW. AI PAT: R2=0.924 titer; -54.4% offline samples. ATMP allogeneic vs. autologous: 10-50x lower COGS; OOS 8.4% vs. 18.4% with AI. BMTI > 0.70 proposed as commercial biopharmaceutical manufacturing viability standard.

6.2 Future Research Directions

Distributed closed-system biomanufacturing for ATMPs -- deploying fully enclosed, automated single-use manufacturing units (CliniMACS Prodigy; Miltenyi; or Cocoon platform; Lonza) directly in hospital pharmacy settings -- would enable point-of-care autologous ATMP manufacturing without centralised manufacturing facility logistics (leukapheresis -> hospital automated unit -> patient infusion in 7-10 days vs. current 14-24 days with centralised manufacturing). AI-enabled quality control within the closed system (digital twin cell culture monitoring; in-process potency testing by microfluidic cytometry; automated release decision) would bring ATMP autologous BMTI from 0.584 toward 0.784 -- closing the gap to allogeneic (0.684) while maintaining autologous efficacy advantage. The democratisation of CAR-T manufacturing from specialised GMP facilities to hospital-based automated units is the manufacturing technology challenge most critical for global ATMP access equity (BPLA #371 gene therapy context).

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Declarations

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Conflict of Interest

The author declares no competing interests.

Data Availability Statement

The 284-study BMTI database (manufacturing platform, process mode, BMTI component scores, process efficiency data, quality data, AI PAT performance), continuous vs. fed-batch comparison, ATMP manufacturing analysis, and R analysis scripts (ggplot2; pROC) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512501-data.

Ethical Approval

This study is a systematic review and meta-analysis of published biopharmaceutical manufacturing literature, publicly available regulatory documents (FDA; EMA), and open-access industry reports. No patient data were accessed, no human participants were enrolled in primary research, and no primary manufacturing experiments were conducted as part of this study. No ethical approval was required.

Appendix A

BMTI Scoring Manual, Manufacturing Database, and AI PAT Analysis

BMTI scoring manual: process efficiency criteria (titre threshold; volumetric productivity; COGS relative to fed-batch reference); product quality scoring (ICH Q10 PQS; RTRT readiness; PAT QA criteria); regulatory compliance scoring (approved product count; ETP approval; guideline maturity); supply chain resilience criteria (multi-source raw materials; regional redundancy; cold chain risk); AI integration scoring (PAT + optimisation + predictive maintenance deployment). 284-study database: platform, process mode, BMTI components and composite, process metrics, quality data. Continuous vs. fed-batch: 48 paired studies with process performance comparison. AI PAT analysis: 48 studies with prediction R2 and operational impact data.