Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence

A Concise Review

by David A. Brindley, Anna L. French, Ricardo Baptista, Nick Timmins, Thorsten Adams, Ivan Wall, and Kim Bure

Methodology, Implications, and Caveats

We compiled a list of key cell therapy bioprocessing technologies through expert-user interviews; reviews of trade and industry literature; and discussions with technology manufacturers. Thereafter, we obtained technical specifications from publicly available documents and (whenever possible) confirmed them with the technology manufacturers (see Acknowledments)to ensure their accuracy.

It was not possible in all cases, however, to make contact with some manufacturers for corroborating publicly available data or obtaining complete data for all technology features sought. Additionally, our data presented are agnostic to performance for particular cell types, are restricted to single-use technologies, and do not reflect the impact of operator skill and/or regulatory restrictions on technology performance. Due to the significant technological heterogeneity in downstream processing technologies, our discussion is restricted to upstream bioprocess technologies concerning cell culture process and media development. We also omitted the impact of cell characterization and testing technologies that may be used alongside those technologies discussed.

Collation of these data clearly demonstrates the convergence of "traditional" biopharmaceutical technologies with the emerging cellular therapies industry. High-level technical specifications are not always easily obtainable. Technology manufacturers are hesitant to definitively state typical operating ranges for reasons of commercial confidentiality. Potential inter–cell-type idiosyncrasies can also make a difference, as well as as-yet limited user experiences and optimization case studies in which cells are the product. In these electronic-only tables, we provide an overview of the most common technologies for rapid and straightforward comparison of available options to guide readers' identification of technologies for further investigation.

Online Table 1 below details process and media development options listed in Figure 1 of the accompanying article (**1**). Online Table 2 below details stirred-tank cell expansion options listed in Figure 1 (**1**). Online Table 3 (next page) details rocking-motion cell expansion options listed in Figure 1 (**1**). Online Table 4 (next page) details adherent-cell expansion options listed in Figure 1 (**1**). And online Table 5 (next page) details other cell expansion options listed in Figure 1 (**1**).

Reference

1 Brindley DA, et al. Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence: A Concise Review. *BioProcess Int.* 12(3) 2014: S##–S##.

ONLINE Table 1: Process and media development (M = manual, A = automated)

				Impeller Types			Control						Liquid Handling		
System	Supplier	Working Volumes	Vessels	Rushton?	Marine?	Gases	Temperature?	pH?	DO?	Gas Flow?	Stir Speed?	Liquids/Vessel	Bolus	Drip	Sampling
Micro-24	Pall	3–7 mL	24	No	No	3	18–45 °C	3.5–8.0	0–100%	0–20 sccm	0–800 rpm	**	M	—	M
ambr 15	TAP Biosystems (Sartorius Stedim)	10–15 mL	24, 48	No	Yes	3	20–40 °C	6.5–7.5	0–100%	0–1 mL/min	300–2,000 rpm	***	A (20 µL–4 mL)	—	A
DASbox	Eppendorf	60–250 mL	4	Yes	Yes	4	10–60 °C	0–14	0–400%	0–25 sL/h	20–3,000 rpm	2	A	A	M
ambr 250	TAP Biosystems (Sartorius Stedim)	100–250 mL	12, 24	Yes (2)	Yes (2)	3	18–55 °C	2.0–8.5	0–200%	0–75 mL/min	150–4,500 rpm	4***	A (30 µL-10mL)	A (10 nL/hr to 120 mL/hr)	A
MiniBio	Applikon	50–800 mL	1	Yes	No	4	Yes	Yes	Yes	Yes	50–2,000 rpm	6	A	A	M
Univessel*	Sartorius Stedim	600–2,000 L	1–4	No	Yes (2)		5–50 °C	6.0–8.0	0–100%	—	—	—	M	—	M
CellReady 3L*	Applikon	1,000–2,400 mL	1	No	Yes	3	Yes	Yes	Yes	Yes	Yes	1–3**	M	—	M

* Single-use vessels that can be integrated with multiple vendor controllers, therefore specifications depend on chosen controller ** Alkali addition *** Limited only by available reagent space

ONLINE Table 2A: Stirred-tank bioreactors for cell expansion (specifications)

					Impeller						Control					
System	Supplier	Working Volumes	Vessel Shape	Sparger	Disk?	Pitched?	Paddle?	Packed Bed?	Agitation Speed	Power Number (nP)	pH	DO	Temperature	Gas Flow	Gases	Peristaltic Pumps
CelliGen BLU	Eppendorf	1.25–40 L	Cylinder	Static	No	Yes	No	Yes	25–200 rpm	1.3	2–14	0–200%	Ambient + 5–40 °C	0.002–7.5 SLPM	8	3
CellReady 200L	Millipore	10–200 L	Cylinder	Static	No	Yes	No	No	0–350 rpm	3.2–4.0	—	—	—	—	—	—
PadReactor	ATMI (Pall)	3–1,000 L	Cube	Dynamic	No	No	Yes	No	*	*	*	*	*	*	*	*
BIOSTAT STR	Sartorius Stedim	12.5–2,000 L	Cylinder	Ring, microsparger	2 × 6	2 × 3	No	No	10–240 rpm	1.3–3.2	5.5–8.5 (single use) 2–14 (reusable)	0–100%	CW + 8–40 °C	0.01–400 L/min	6	2 or 3

* Open architecture — dependent on the controller chosen

ONLINE Table 2B: Stirred-tank bioreactors for cell expansion (benefits)

			Automation Capabilities								Sensor Technologies/PAT					GMP Compliance		
System	Supplier	Performance (CHO maximum density)	Process Parameters	Trends	Temperature Control?	pH Control?	DO Control?	Agitation Control?	Gas Mix?	Media and Supplement Addition?	Analog Inputs	Analog Outputs	Traditional pH?	Single-Use Optical pH?	Conventional DO?	Single-Use DO?	Weighing Scale?	Vessel Material (USP Class VI or higher)	SCADA	Validation Packages
CelliGen BLU	Eppendorf	8.58×10^6	32	8	Yes	Yes	Yes	Yes	3–4	Yes	7	7	Yes	Yes	No	Yes	Yes	Polycarbonate	BioCommand	Yes
CellReady 200L	Millipore	$>20 \times 10^6$	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PadReactor	ATMI (Pall)	$10–20 \times 10^6$	—	—	Yes	Yes	Yes	Yes	No	Yes	—	—	Yes	Yes	Yes	Yes	No	TK8	—	Yes
BIOSTAT STR	Sartorius Stedim	160×10^6	unlimited	16	Yes	Yes	Yes	Yes	Yes	Yes	4	4	Yes	Yes	Yes	Yes	Yesccccc	ultra-low density polyethylene (ULDPE)	BioPAT MFCS	Yes

* No data available

ONLINE Table 3A: Rocking-motion bioreactors for cell expansion (specifications)

						Control								Liquid Handling	
System	Supplier	Working Volumes	Weight Measurement?	O_2/Air	CO_2/Air	Rocker Speed	Rocker Angle	Rocking Control?	pH?	DO?	Temperature	Gas Flow	Gases	Pump Flow	Pumps
WAVE 2/10	GE Healthcare	0.1–5 L	Yes	0–50%	0–12%	2–40 rocks/min	2–12°	No	Yes	Yes	0–50 °C	—	—	—	—
XRS	Pall Life Sciences	2– 20 L	No	—	—	1–35 rpm	—	Biaxial	6–8	0–200%	Ambient + 8–40° C	—	3	—	3
Xuri W25	GE Healthcare	0.3–25 L	0.5–25 kg	0–50%	0–15%	2–40 rpm	2–12°	Yes	6.0–8.0	0–100%	20–40 °C	0–1,000 mL/min	—	0.07–100 mL/min	—
BIOSTAT RM	Sartorius Stedim	0.1–300 L	Yes	0–100%	0–100%	2–42 rpm	4–10°	Yes	6.5–8.5	0–100%	CW + 8–40 °C	0.02–10 L/min	4	0.01–180 mL/min	4
WAVE 200 and 500/1000	GE Healthcare	10–500 L	No	0–50%	0–15%	4–25 rocks/min	0.5–9°	No	Yes	Yes	5–40 °C	—	—	—	—

ONLINE Table 3B: Rocking-motion bioreactors for cell expansion (benefits)

			Performance (maximum CHO density)	Rocking Profiles?	Automated Perfusion?	GMP Compliance								
System	Supplier	Footprint				Vessel Material (USP Class VI or higher)	On-Board Control?	Remote PC Control?	Units Linked to One PC	SCADA	User Access Levels	Alarms	OPC	Validation Packages
WAVE 2/10	GE Healthcare	489 × 330 × 200	10×10^6	Yes	Yes	ethylene vinyl acetate (EVA)/low density polyethylene copolymer	X	No	0	—	No	No	No	Yes
XRS	Pall Life Sciences	*	*	*	*	*	*	*	*	*	*	*	*	*
Xuri W25	GE Healthcare	475 × 430 × 60; 800 × 610 × 260	—	Yes	Yes	Yes	No	Yes	32	UNICORN DAQ	Yes	Yes	Yes	Yes
BIOSTAT RM	Sartorius Stedim	—	—	Yes	2	Yes	Yes	Yes	16	BioPAT MFCS	Yes	Yes	Yes	Yes
WAVE 200 and 500/1000	GE Healthcare	—	—	No	No	8	Yes	No	—	—	No	No	No	NO

* No data available

ONLINE Table 4: Adherent-cell technologies for cell expansion

								Control							Detection			
System	Supplier	Surface Area	Labware	Material	Closed?	Perfusion?	Pumps	Agitation Speed	pH	DO	Temperature	Media Flow	Gases	Cell Density	Growth Curve?	Morphology	Control	GMP Compliant?
Quantum	Terumo BCT	21,000 cm^2	Proprietary Bioreactor	Hollow-fiber	Functionally	N/A	1	NA	N/A	N/A	—	—	1	—	—	—	Touchscreen	Yes
iCELLis	ATMI (Pall)	53–50,000 cm^2	Fixed-bed, microfibers	USP class VI rigid plastic	Yes	Yes	1–5	0–1,500	6.0–9.0	0–100%	15–40	—	4	—	—	—	PC	Yes
ACFM	Thermo/Nunc	75,840–101,120 cm^2	Cell Factory 10 (4 × 3), Cell Factory 40 (4 × 1)	USP class VI polystyrene	Yes	N/A	1	NA	—	—	—	—	—	—	—	—	On-board	Yes
Xpansion	ATMI (Pall)	6,120–122,400 cm^2	Proprietary plate	USP class VI polystyrene	Yes	Yes	2	5–250 rpm	6.0–9.0	0–150%	0–50	1–5 mm/s	4	Holographic microscope	Yes	Holographic microscope	PC	Yes
CellBase CT	TAP Biosystems (Sartorius Stedim)	75–157,500* cm^2	T75, T175, Triple, HYPER*	USP class VI polystyrene	Functionally	N/A	10	NA	N/A	N/A	30	N/A	1	Trypan Blue	Essen Incucyte	Essen Incucyte	PC	Yes

* Based on research-grade experience

ONLINE Table 5: Other technologies for cell expansion

System	Supplier	Technology
CellMaker Plus	Celluxus Ltd.	Airlift
BelloCell-500P	CESCO Bioengineering	Microcarrier
Air-Wheel bioreactor	PBS Biotech	Air-Wheel
G-Rex	Wilson Wolf	Static

Figure 1: Overview of commercially available single-use cell bioprocessing technologies