

## ▶ Which Process Option is Right for Me?

### A Comparison of Fed-Batch, Perfusion and Concentrated Perfusion

When determining how to develop a bioprocess for your drug candidate, there are many key decisions about how to proceed including choosing a cell line, whether to outsource or keep in-house, and what type of bioprocess is most economic.

The old fed-batch and perfusion processes are well known but both have limitations. If you wish to move to a modern production platform, which one is best?

If you already have a facility this will impact significantly your cost base and therefore your choice, but today, most people wish to evaluate all opportunities that could reduce the cost of development and the cost of manufacture. Here is an overview about the four main process options commonly available. (note that batch processing is ignored here)

#### Typical questions may include:

Should I use fed-batch rather than perfusion? Which is lower cost? Which involves less risk?  
What about the new concentrated perfusion processes?  
How do I know which process option is right for me?

...here are some ideas and answers.

### Perfusion, Concentrated Perfusion and Fed-Batch

#### Use Perfusion if you want to:

- keep a low cell density of 30m or less for reasons of cell or product stability, for example because the concentration of a required toxic molecule will be too difficult to control.
- replicate a process that is moving from older style perfusion technology, such as a spin filter or cell settler, and just wish to benefit from the ATF System's improved reliability and gain a filtered product stream - but wish to maintain a similar cell density as previously.

#### Use Concentrated Perfusion (ATF-perfusion™) if you want to:

- generate a high cell density of 70-200m to generate high daily production titres (e.g. >1g/L/day)
- reduce the size of bioreactor required to produce to same amount of product as in fed-batch or perfusion
- reduce the time taken to produce X kilograms of your molecule
- reduce USP development times
- standardize process control and improve the reliability of reactor performance
- reduce the complexity of media development and use only a single medium feed
- remove contaminants and by-products from the reactor and improve product quality
- maintain a constant environment for cell growth and/or product expression
- utilize an existing DSP train that is suited to receive one or two vessel volumes per day of clarified material at 1-2g/L concentration.
- take advantage of moving towards continuous processing in downstream activities

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#### Use Fed-Batch if you want to:

- utilize effectively your existing 10,000L or 20,000L reactor

#### Comparison Table

Perfusion	Concentrated Perfusion	Fed-Batch
Feed medium	Complete medium medium	Complete medium (multiple)
Environment	Constant	Constant
Osmolarity change	Constant	Constant
Waste / toxic molecules	Removed	Removed
Product residence time	Low	Low
Stability of environment for product	High	High
Typical Process Duration	1-2 months	1-2 months
Typical cell concentration	10-30m	60-120m
Typical cell viability during production	75-95%	75-95%
Typical cell viability at harvest	75-95%	75-95%
Compatible with disposable reactors?	Yes	Yes
Compatible with ATF-cellbanking™?	Yes	Yes
Compatible with ATF-manufacturing™?	Yes	Yes

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Perfusion	Concentrated Perfusion	Fed-Batch
Seed train (liters) 1ml (vial), 5ml, 25ml, 125ml, 600ml, 3L, 15L, 75L	8 Stages: 1ml (vial), 5ml, 25ml, 125ml, 600ml, 3L, 15L, 75L	8 Stages: 1ml (vial), 5ml, 25ml, 125ml, 600ml, 3L, 15L, 75L, 400L, 2000L
Seed train with ATF-manufacturing™ Platform (liters)	2 Stages: 100ml (bag), 10L	2 Stages: 100ml (bag), 10L
Typical manufacturing vessel size	500L	500L
Media cost per litre	Moderate	Moderate
Media volume required	High (1-2vvd)	High (1-2vvd)
Harvest	Daily / constant	Daily / constant
Process control requirements	High	High
Operational skill required	High	High
Alkali addition	Low	Low
§Compatible with continuous DSP	Yes	Yes
Output from 1000L reactor, per day	0.2kg	0.8kg
§Output from 1000L reactor, per run (CHO cell data)	6kg (20m cells per ml) (30 days)	24kg (80m cells per ml) (30 days)
Time to produce 10 Kg of product	1-2 Batches ~7 weeks	1 Batch ~2 weeks
Yearly output from 1000L reactor	60kg (10 runs)	240kg (10 runs)
Reactor size required to produce ~250Kg per year	4x 1,000L	1x 1,000L

§ Model data taken from CMC ICOS webinar 2009 presented through Bioprocess International (available in the download center) and from one of Refine Technology's pharmaceutical clients

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Process Comparison Table by Minnesota University

	Perfusion *	Concentrated Perfusion **	Fed-Batch *
Scale	400L	400L	15,000L
Length	50-180 days	30-60 days	15-20 days
Cell Density	6-100 x 10 <sup>6</sup>	60-120 x 10 <sup>6</sup>	6-10 x 10 <sup>6</sup>
Cell Line Stability	-	-	+
Product Concentration	+/-	+	+
Productivity	+	+	+
Product Residence Time	+	+	-
Process Simplicity	-	-	-
Process Control	-	-	-
Contamination Risk	-	-	+
Operation Costs	+	+	+/-

\* Data from CD-ROM Cell Retention and Perfusion, by Chun Zhang, Cell and Tissue Reactor Engineering, © 2003 University of Minnesota

\*\* Data estimated on similar basis by Refine Technology