Intensification Of A Platform Fed-Batch Process – A CDMO Perspective

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Introduction

In recent years CHO-based biopharmaceutical mAb process designs have converged and today rely on similar infrastructures and protocols. Typically, cells are expanded in a series of batch cultivations in shake flasks, rocking-motion and stirred-tank bioreactors to generate sufficient cell counts for the inoculation of a production bioreactor. Production bioreactors are usually operated in fed-batch mode employing basal medium complemented by static addition of feed solution(s). Respective processes commonly reach a max. of 15-25 MVCmL^{-1} and 3-5 gL^{-1} of mAb in ~14 days [1,2,3]. Lately, increasing demand for biopharmaceuticals has led to the advent of new intensified process designs [1]. These intensified processes enable higher max. VCCs and IVCCs yielding mAb titers beyond 5 gL^{-1} in 8 to 12 days but often integrate new technologies that require changes to the existing manufacturing infrastructure and thus may be difficult and/or costly to implement [1,2,3]. This work demonstrates intensification of a CHO-based mAb process leveraging existing fed-batch manufacturing facilities by implementing an intensified seed train and a dynamic feeding strategy based on commercial fed-batch media and feed solutions delivering a cost efficient intensified bioprocess design.

Cost efficiency

The more the better? The answer depends on the perspective. Undoubtedly, higher titers come at a price. Intensified bioprocess designs scale IVCC (rather than q_p) to increase the STY, that is, gram of product per liter and day. The required high VCCs are usually generated in perfusion cultivations, which are associated with extra material and/or consumable cost. The right balance between output and cost per batch, that is, cost efficiency, depends on a number of factors, e.g., the production scale, clinic vs. market supply, … and in the end also on the CDMO.

Parameter	Unit	Conv.	IFB 1.2	IFB 5	IFB 30	HPFB
Product titer	gL^{-1}	5.0	5.0	5.0	5.0	5.0
Product amount	x	1.0	1.0	1.0	0.9	0.9
Time in production bioreactor	d	16	12	11	7	9
No. of FTEs	x	1.0	0.6	1.0	1.2	1.2
Material cost	x	1.0	0.7	1.8	1.8	3.0
Consumable cost	x	1.0	1.0	1.5	2.5	2.5
No. of batches per year	x	1.0	1.3	1.8	2.3	1.8
Profit per batch	x	1.0	1.0	1.0	0.9	0.9
Costs per batch	x	1.0	0.8	1.8	2.2	2.2
Cost efficiency	**x**	**1.0**	**1.8**	**1.0**	**1.2**	**0.7**

Table 1: Cost efficiency estimates of different intensified bioprocess formats in comparison to a conventional fed-batch process.

From conventional to intensified bioprocess designs

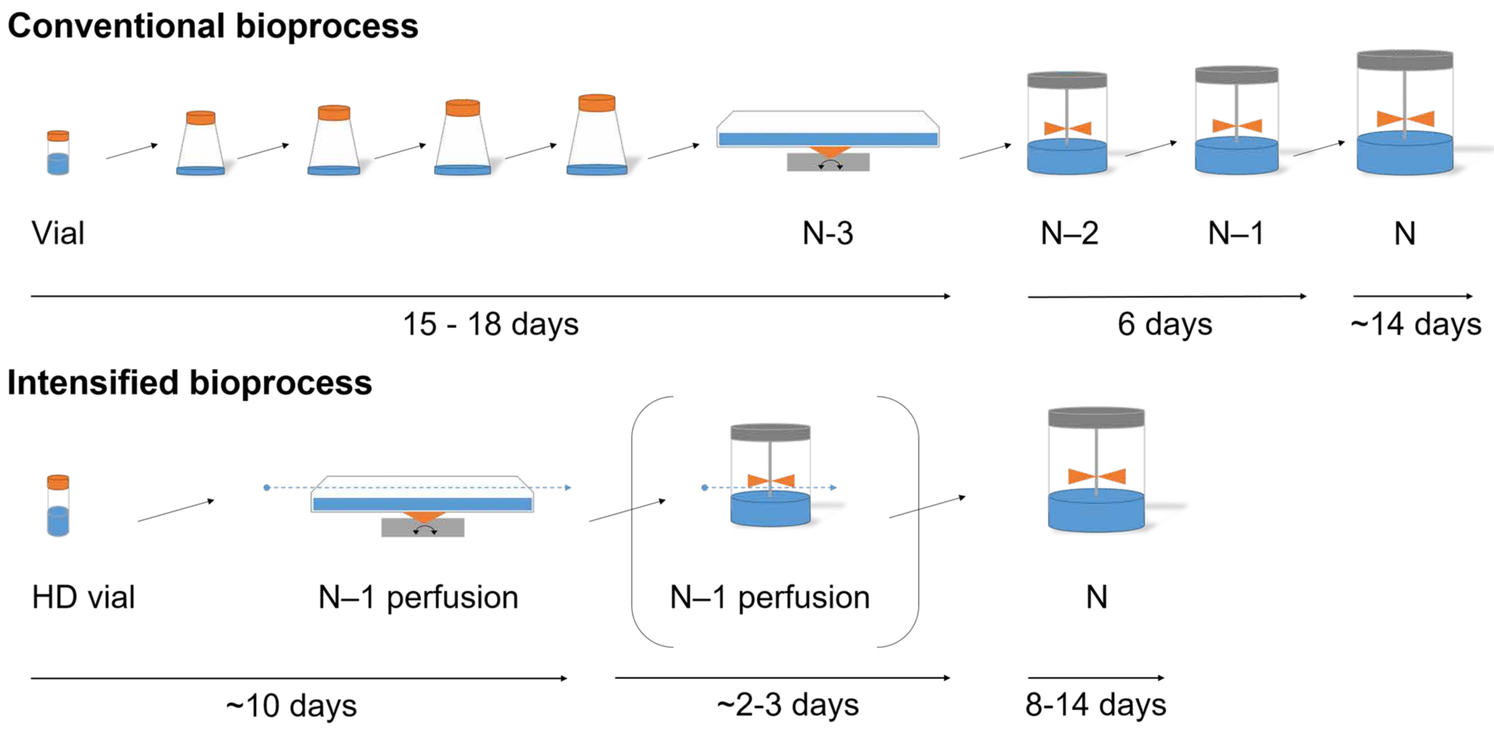

Figure 1: Timelines for conventional and intensified bioprocess designs. A conventional bioprocess train starts with the thawing of a vial with 1 mL and 10 MVCmL^{-1} and continues with several expansion steps in shake flasks, rocking-motion and stirred-tank bioreactors. The production bioreactor has a seeding concentration of 0.3 MVCmL^{-1} and a run-time of 14 days. The intensified bioprocess design starts with thawing of a HD vial with 4.5 mL and 100 MVCmL^{-1} and continues with a single expansion step in a rocking-motion system operated in perfusion. The production bioreactor has a seeding concentration between 1.2 and 30 MVCmL^{-1} and a run-time of 7 to 14 days. Optionally, a second seed bioreactor, operated in perfusion mode, is implemented.

Process performance of intensified bioprocess designs

Conventional biopharmaceutical processes comprise a growth and a production phase. The concept of intensified bioprocess designs is to condensate the growth phase and quick start into the production phase. Therefore, much higher seeding concentrations are applied, necessitating the development of feeding strategies beyond a static bolus scheme. Here, we developed a dynamic and continuous cell-specific feeding scheme that enables virtually unlimited scaling of the seed concentration and yields high max. VCCs and product titers in different intensified bioprocess designs.
Considering a benchmark product titer of 5.0 gL^{-1} IFB 30 reduces the batch time from 16 days to 7 days (Table 1 and Figure 2: Conventional vs. IFB 30) but creates high material and consumable costs due to a second seed train stage. IFB 1.2 reduces the batch time by 4 days and provides the best cost efficiency, as the production bioreactor is directly inoculated from the N-1 stage.

First, an intensified seed train was established involving HD cell banks and a rocking-motion bioreactor. Cells were grown in perfusion mode utilizing a custom-made perfusion media based on a blend of commercial fed-batch media and feed solutions. Cells inoculated an intensified process with seeding concentrations between 1.2 and 30 MVCmL^{-1}. Continuous and dynamic cell-specific feeding was employed to support optimal cell growth and productivities.

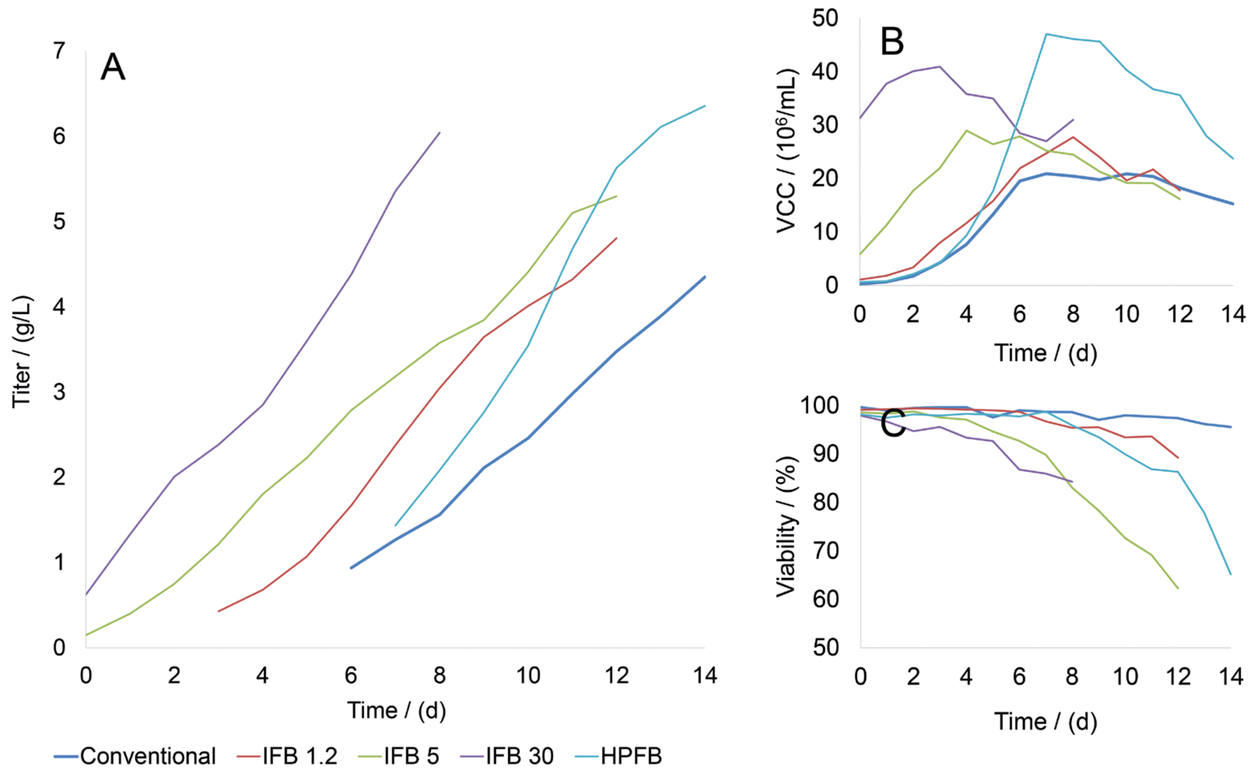

Figure 2: Process performance of conventional and intensified bioprocess formats, respectively. (A) Product titer, (B) Viable cell concentration (VCC) (C) Cell viability. Seeding concentrations of conventional and HPFB bioprocess was 0.3 MVCmL^{-1}. Seeding concentration of IFB bioprocesses was 1.2, 5.0, or 30.0 MVCmL^{-1}, respectively.

Conclusion

Intensified bioprocess designs can significantly reduce batch time without compromising product titers. However, they come at a price. Assessing overall cost efficiency is therefore utterly important. Depending on the existing infrastructure, the project phase (clinic vs. market supply), or the projected production scale, the best process design may look different. Here, we executed different intensified bioprocess designs with the objective to reach a product titer of 5 gL^{-1} and estimated their cost efficiency. IFB 1.2 showed the best balance between profit and cost per batch. The respective intensified bioprocess design reduces the batch time by ~25%, and simultaneously lowers the costs per batch by 20%.
The more the better? The right answer is: ‘not necessarily’. Cost efficiency and process performance are equally important when assessing the right bioprocess design.

Abbreviations

HPFB	Hybrid perfusion fed-batch
IFB	Intensified fed-batch
IVCC	Integral viable cell concentration
MVC	Million viable cells
STY	Space-time yield
VCC	Viable cell concentration
q_p	Cell-specific productivity