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Application Note

Improving fed-batch yields by combining EX-CELL® Advanced and Cellvento® cell culture media portfolios

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Abstract

The biopharmaceutical industry is interested in developing high-titer fed-batch processes to meet increasing market demands and reduce manufacturing costs. While these processes can achieve increased cell densities which support improved volumetric productivity, they also have high nutrient demands. Nutrient limitations can be prevented with addition of a highly concentrated feed at different time points during the culture to help sustain the production phase. Given the diversity of media platforms, Chinese hamster ovary (CHO) cell characteristics and process settings, establishing a cost- and time-efficient approach for process optimization is essential. This application note provides guidance and options for improving culture yield with off-the-shelf catalog products. Media combinations, dynamic fed-batch feeding options, and feed screening strategies suitable for diverse cell lines and manufacturing scenarios are presented.

Introduction

The biopharmaceutical industry primarily uses fed-batch methods, rather than continuous or perfusion approaches, to produce stable monoclonal antibodies (mAbs) and next generation biopharmaceuticals from CHO cells. Manufacturing titers have steadily improved over the last 40 years from tens of mg/L to 10 g/L primarily through cell line engineering, media development, and process control improvements achieving higher specific productivities (qp), increased peak viable cell densities (VCD), and prolonged production durations. Further increases in volumetric productivity have been reported, which indicates that there is still potential for additional cost reductions using fed-batch operations.

A critical step for developing a fed-batch process is selecting an appropriate medium and feed. The most suitable medium and feed for each CHO cell line, manufacturing process, and/or therapeutic protein must be determined. Given the variety of media and feeds available on the market, evaluation of multiple options from different vendors is a common way to determine what fed-batch system represents the best option for a particular CHO cell platform. In addition to screening fed-batch systems from different vendors, media from one supplier may be evaluated in combination with a non-companion feed from another. In some cases, a multipart medium and/or feed from multiple vendors is evaluated. This approach speaks to the diversity of CHO cell lines beyond the historical lineages of CHO-S, CHO-DG44, and CHO-K1. The platforms that exist within the biopharmaceutical industry, along with the individual clones produced from those platforms, vary greatly in nutrient requirements and performance. With little knowledge of the actual composition of medium and feed formulations on the market and with a need to use screening time effectively, all available options must be evaluated to optimize the strategy. While this approach can be effective, it may result in a situation where different vendors are supplying medium and feed, leading to increased supply chain risk.

Because different CHO platforms and clones vary in their nutrient requirements, medium and feed formulations and feeding strategies have to be screened, designed and optimized for each clone. The EX-CELL® Advanced and Cellvento® Fed-batch platforms are animal component free, chemically defined cell culture media and companion feeds designed for CHO cell-based bioproduction.

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Each unique production medium was designed to support initial cell growth and productivity while each unique companion feed, containing a proprietary formulation of amino acids, vitamins, trace metals, salts and other components, was designed to replenish depleted nutrients required for cellular function and to maintain the production phase during biotherapeutic manufacturing.

Because no single fed-batch system will perform optimally for all CHO cells, these systems were independently developed for use with CHOZN® GS-/-, CHO-S, CHO-DG44, and CHO-K1 cell expression systems. Owing to the independent development of these two systems, they offer distinct approaches to the fed-batch process and are uniquely positioned for use in combination.

The EX-CELL® Advanced Fed-batch platform was designed based on years of experience with multiple CHO cell lines from different sources to yield superior growth, production, and longevity by replenishing depleted nutrients. This platform delivers a diverse set of nutrients to satisfy cellular requirements and is an integral part of the CHOZN® Expression Platform.

More information on the use of EX-CELL® Advanced Medium and Feed in the CHOZN® Expression Platform can be found in "CHOZN® Cell Line Platform Technical Bulletin."

The CHOZN® platform can also be integrated with the UCOE® expression technology to accelerate biopharmaceutical development by increasing the efficiency of isolating high producing clones. The power of CHOZN® and UCOE® is demonstrated in "Accelerating Cell Line and Process Development."

The Cellvento® Fed-batch platform was designed to provide a highly concentrated one-part feed meant to reduce total feeding volume. This single part system takes the place of a two part feed system which included a main feed and an additive feed of critical amino acids that required high pH for dissolution. The critical amino acid components are now incorporated into the main feed with modifications enabling them to be added at neutral pH to the culture. With Cellvento® 4Feed, component solubility and stability challenges were overcome and a neutral final pH was achieved.

Cellvento® 4CHO and EX-CELL® Advanced Medium are recommended for use with all CHO cell lines. Additional guidance on use of these products along with other current generation catalog formulations can be found in "CHO Cell Culture Media & Feeds Selecting the Right Media to Enable Your Next Breakthrough."

Evaluation of Media and Feeds

Screening multiple medium and feed pairs offers one of the best ways to arrive at an optimal fed-batch combination for a given cell line. While the EX-CELL® Advanced and Cellvento® Fed-batch platforms are superior products on their own, combining these platforms offers even more opportunities to arrive at the optimal combination of medium and feed(s). By screening the relatively small number of combinations of media and feeds from the EX-CELL® Advanced and Cellvento® Fed-batch platforms, an improved fed-batch combination can be identified. If design space is limited, Table 1 outlines the minimal set of test conditions used in Study 1 to evaluate these two systems alone and in combination.

Table 1: Medium and feed combinations evaluated in Study 1

Medium	Feed
EX-CELL® Advanced CHO Fed-batch Medium	EX-CELL® Advanced CHO Feed 1
EX-CELL® Advanced CHO Fed-batch Medium	Cellvento® 4Feed
EX-CELL® Advanced CHO Fed-batch Medium	50:50 ratio of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed
Cellvento® 4CHO	Cellvento® 4Feed
Cellvento® 4CHO	EX-CELL® Advanced CHO Feed 1
Cellvento® 4CHO	50:50 ratio of Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1

Table 2: Example 50:50 feeding strategy for a 14 day fed-batch process

Feed	Day 3	Day 5	Day 7	Day 10	Day 12	Total
EX-CELL® Advanced CHO Feed 1	2.5%	2.5%	3.75%	3.75%	2.5%	15%
Cellvento® 4Feed	2.5%	2.5%	3.75%	3.75%	2.5%	15%
Total Feed	5%	5%	7.5%	7.5%	5%	30%

The 50:50 mixture of feeds listed in Table 1 can be delivered by combining the individual liquid feeds into a single mixture prior to supplementing or by feeding each individually. By creating a single liquid mixture, a single feed operation is possible. Table 2 provides an example of a representative 50:50 feeding strategy for the feeds when used independently. Given the differences in feed characteristics, along with the variability in nutrient requirements and behaviors of every cell line, additional ratios of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed should be examined if design space permits or as a follow up study. Additional ratios can include 75:25 and 25:75 along with 67:33 and 33:67 if desired. The single mixture of these feed ratios can be stored, protected from light, at 2-8°C for up to 30 days.

Table 3: Recommended feed volumes and frequency ranges

Feed	Recommended volume	Recommended frequency
EX-CELL® Advanced CHO Feed 1	5-10% v/v	48-72 hour
Cellvento® 4Feed	1-6% v/v	48-72 hour
50:50 ratio of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed	3-10% v/v	48-72 hour

While typical feed volumes and frequency ranges are provided in Table 3, it is recommended that the needs of each cell line be empirically determined. Product information sheets for the EX-CELL® Advanced CHO Fed-batch platform and Process Guidance for Cellvento® 4CHO Fed-batch platform offer initial feeding parameters. Following an initial evaluation of the medium and feed(s), a follow up study should be conducted to determine optimal volumes and timing for a given cell line.

Case Studies: Evaluation of mAb Expressing CHOK1 and CHOZN® Cell Lines Cultured using EX-CELL® Advanced and Cellvento® Media and Feeds

The following case studies evaluated whether synergies could be achieved through combining the EX-CELL® Advanced and Cellvento® Fed-batch Systems using CHOK1 and CHOZN® cell lines expressing proprietary mAbs. These studies determined whether improvements in cell growth, culture longevity, and productivity where possible.

Initial studies were conducted in 50 mL spin tubes, as this system offers high throughput and is scalable to bioreactors. This approach also permits near simultaneous analysis of multiple experimental conditions. Shake flasks, deep well plates, and micro-bioreactors are other suitable platforms with which to conduct evaluation studies. The final study was conducted in a Mobius® 50L Single-Use Bioreactor.

In the first study, both the EX-CELL® Advanced and Cellvento® Fed-batch systems were evaluated separately and in combination (Table 1). The second study builds upon the data generated utilizing the 50:50 mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed identified in Study 1 and explores additional ratios of the two fed-batch feeds. Scalability of the 50:50 mixture approach was confirmed in the third study.

Materials

1. CHOK1 cell host expressing proprietary mAb (CHOK1 mAb1) and CHOZN® ZFN-modified GS-/- CHO Cell Line expressing a different proprietary mAb (CHOZN® mAb2). The CHOZN® mAb2 cell line utilizes a plasmid containing UCOE® elements alongside mAb2, helping to achieve high volumetric productivity.
2. EX-CELL® Advanced CHO Fed-Batch Medium pH 7.2 **Cat. No. (24366C)**
3. EX-CELL® Advanced CHO Feed 1 pH 8.5 (without glucose) **Cat. No. (24368C)**
4. Cellvento® 4CHO pH 7.0 **Cat. No. (103795)**
5. Cellvento® 4Feed pH 7.0 **Cat. No. (103796)**
6. Glucose stock solution (400 or 450 g/L)
7. Climo-Shaker ISF1-XC - 320 rpm, 25 mm orbital, 37°C, 5% CO_2, 80% relative humidity
8. TubeSpin® Bioreactor 50

9. ViCell™ XR counter - viable cell density and viability determination
10. ForetBio Octet® QKe system - mAb quantitation of small scale experiments
11. Mobius® 50L Single-Use Bioreactor

For small scale experiments, cell count, viability and volumetric productivity were determined on specified days using a ViCell™ XR counter and ForetBio Octet® QKe system. Productivity was determined using a standard curve generated from a representative mAb. Individual conditions were maintained until day 14 (no condition had a cell viability drop below 70%), at which time the experiment was terminated. All small-scale data points shown are the average of biological duplicates. For the bioreactor experiment, volumetric productivity was determined using a HPLC based methodology and single data points are shown.

It is important that the media used during cell expansion and production are the same or known to be compatible. In this case, cell lines were adapted to each medium for at least 3 passages, cells were expanded and the fed-batch performed in the same medium. Refer to the product information sheets for the EX-Cell® Advanced CHO Fed-batch Platform and Process Guidance for Cellvento® 4CHO Fed-batch Platform.

Study 1: Establishing the effectiveness of combining EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed

The first study was established using the conditions described in Table 4. Specifically, the CHOK1 mAb1 cell line expressing a proprietary mAb was grown in 50 mL spin tubes where multiple medium and feed combinations were evaluated. The study design paired EX-CELL® Advanced and Cellvento® products, evaluated the possible usefulness of a 50:50 combined feed and maintained the individual fed-batch controls. The feeding schedule utilized for the 50:50 mixture was dictated by the medium used and aligned with the schedule used by each system's feed.

Table 4: Experimental conditions and operating parameters used in Study 1

Experimental Condition	Operating Parameter
Culture Vessel	TubeSpin® Bioreactor 50
Initial Working Volume	30 mL
Inoculation Density	3 x 10^5 viable cells/mL
Harvest Criterion	End culture after 14 days or when viability < 70%
Sampling Points	Study days 3,5,7,10,12,14
Sampling Volume	≤ 1800 µL per day (depending on analysis needed)
Glucose Addition	On sample days, feeding to levels ≥ 6 g/L
Feed Schedule 1 (EX-CELL® Advanced CHO Feed 1)	5% Day 3, 10% Day 5,7,10, 5% Day 12
Feed Schedule 2 (50:50 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed) Medium = EX-CELL® Advanced CHO Fed-Batch Medium	5% Day 3, 10% Day 5,7,10, 5% Day 12 (each feed was fed independently at half the days total; feeds were not combined into a single liquid mixture)
Feed Schedule 3 (Cellvento® 4Feed)	3% Day 3,5, 6% Day 7, 3% Day 10,12
Feed Schedule 4 (50:50 Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1) Medium = Cellvento® 4CHO	3% Day 3,5, 6% Day 7, 3% Day 10,12 (each feed was fed independently at half the days total; feeds were not combined into a single liquid mixture)

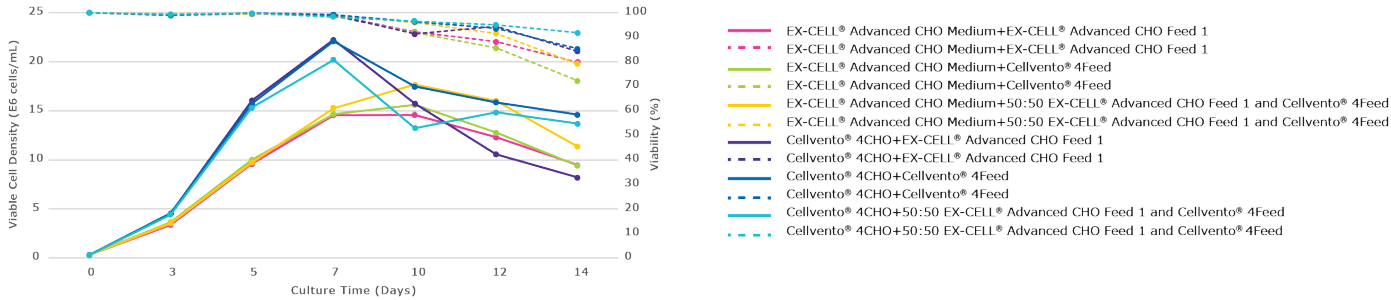

Figure 1A

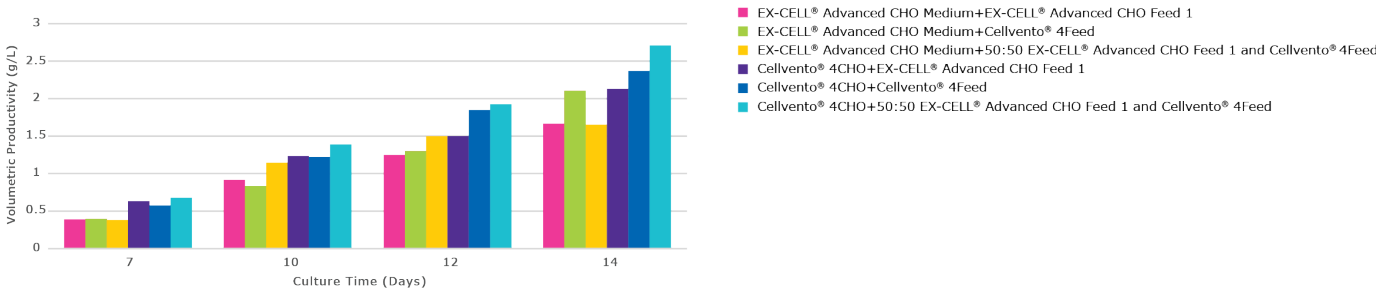

Figure 1B

Figure 1: (A) Viable cell density (solid lines), viability (dashed lines) and (B) volumetric productivity during the 14 Day fed-batch process for CHOK1 mAb1 cultured in Cellvento® 4CHO and EX-CELL® Advanced CHO Medium with each single feed and mixed (50:50) feed.

The growth curves **(Figure 1A)** were clustered into two groups depending on the medium used. Conditions containing EX-CELL® Advanced CHO Fed-Batch Medium grew more slowly and had peak viable cell densities between 14.5 and 17.5x10^6 cells/mL on day 10. Conditions containing Cellvento® 4CHO medium grew more quickly and had peak viable cell densities between 20 and 22x10^6 cells/mL on day 7. The impact of the feed on growth was dependent upon the medium with no universal pattern for this clone. The viability curves **(Figure 1A)** express similar cell line preferences as those seen for viable cell density. Prolonged viability was generally observed for CHOK1 mAb1 in the conditions containing Cellvento® 4CHO medium. The volumetric productivity **(Figure 1B)** varied significantly with each experimental condition. For CHOK1 mAb1, Cellvento® 4CHO medium yielded the highest productivity when fed 50:50 Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1 while EX-CELL® Advanced CHO Fed-Batch Medium yielded the highest productivity when fed Cellvento® 4Feed. These top producing conditions did not correspond with the highest peak viable cell densities **(Figure 1A)** suggesting that the feeds provided some nutrients required for production but not for growth. After 14 days, the highest producing combination, Cellvento® 4CHO medium fed 50:50 Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1, yielded over 45% more product than the lowest producing combination, EX-CELL® Advanced CHO Fed-Batch Medium fed EX-CELL® Advanced CHO Feed 1.

The results of this case study revealed that for this cell line, the best medium and feed combination was Cellvento® 4CHO and 50:50 Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1. This combination resulted in higher volumetric productivities than the individual fed-batch systems used as directed in their respective product information/process guidance documents. This study validated this approach as a method for potentially obtaining superior performance through a unique combination of medium and feed. While Cellvento® 4CHO and 50:50 Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1 showed the best performance in this study, opportunities still exist to further optimize medium and feed performance by varying the feed ratio, volumes and/or timing of administration.

Study 2: Evaluating the impact on performance of varying the ratio of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed

The second study used the conditions described in Table 5. Both the CHOK1 mAb1 cell line used in the first study and the higher producing CHOZN® mAb2 cell line producing a different proprietary mAb were grown in 50 mL spin tubes. The study design builds upon the work of Study 1 by evaluating additional feed ratios to determine if there was a universally optimum ratio of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed or if the optimum ratio depends upon the cell line used. The impact of media could also be further evaluated through the continued use of both EX-CELL® Advanced CHO Fed-Batch Medium and Cellvento® 4CHO.

Table 5: Experimental conditions and operating parameters used in Study 2

Experimental Condition	Operating Parameter
Culture Vessel	TubeSpin Bioreactor 50
Initial Working Volume	30 mL
Inoculation Density	3 x 10^5 viable cells/mL
Harvest Criterion	End culture after 14 days or when viability < 70%
Sampling Points	Study days 3,5,7,10,12,14
Sampling Volume	≤ 2300 µL per day (depending on analysis needed)
Glucose Addition	On sample days, feeding to levels ≥ 6 g/L
Feed Schedule 1 (Cellvento® 4Feed)	3% Day 3,5, 6% Day 7, 3% Day 10,12
Feed Schedule 2 (All EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed mixtures)	5% Day 3,5, 7.5% Day 7,10, 5% Day 12 (liquid feeds were mixed prior to administration)
Feed Schedule 3 (EX-CELL® Advanced CHO Feed 1)	5% Day 3, 10% Day 5,7,10, 5% Day 12

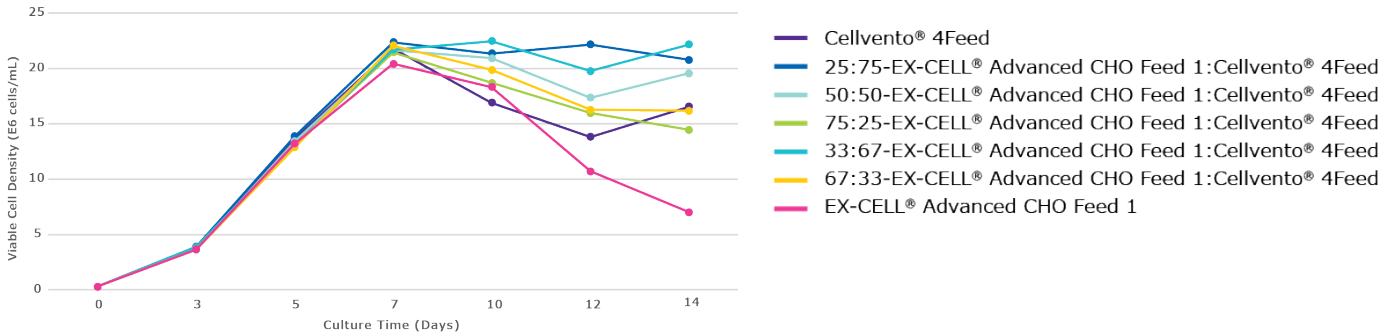

Figure 2A

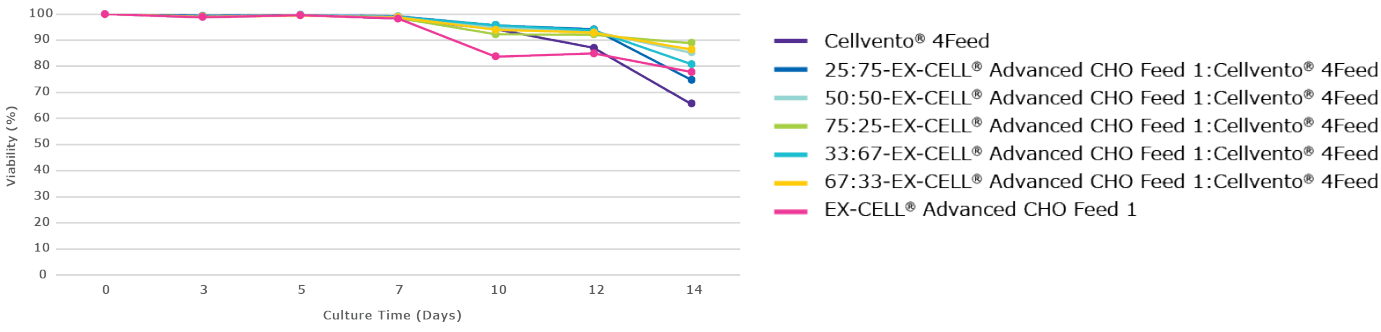

Figure 2B

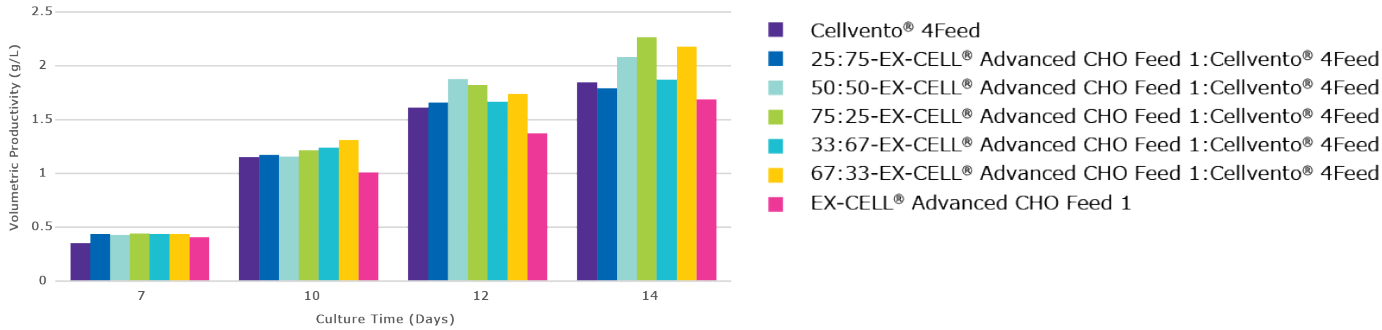

Figure 2C

Figure 2: Viable cell density (A), viability (B), and volumetric productivity (C) during the 14 Day fed-batch process for CHOK1 mAb1 cultured in Cellvento® 4CHO.

CHOK1 mAb1 cultured in Cellvento® 4CHO showed a preference for feed mixtures containing higher amounts of EX-CELL® Advanced CHO Feed 1. Cultures fed mixtures high in EX-CELL® Advanced CHO Feed 1 experienced slightly better longevity and increased productivity as compared to mixtures high in Cellvento® 4Feed. EX-CELL® Advanced CHO Feed 1 alone experienced an earlier drop in viability **(Figure 2B)** and, as such, productivity was less than mixtures containing at least some Cellvento® 4Feed. Peak viable cell density was similar for all mixtures **(Figure 2A)**. While mixtures high in Cellvento® 4Feed maintained high viable cell density for a longer time, that higher VCD did not translate into more production **(Figure 2C)**. CHOK1 mAb1 cultured in EX-CELL® Advanced CHO Fed-Batch Medium showed similar preferences for mixtures containing high amounts of EX-CELL® Advanced CHO Feed 1 (data not shown).

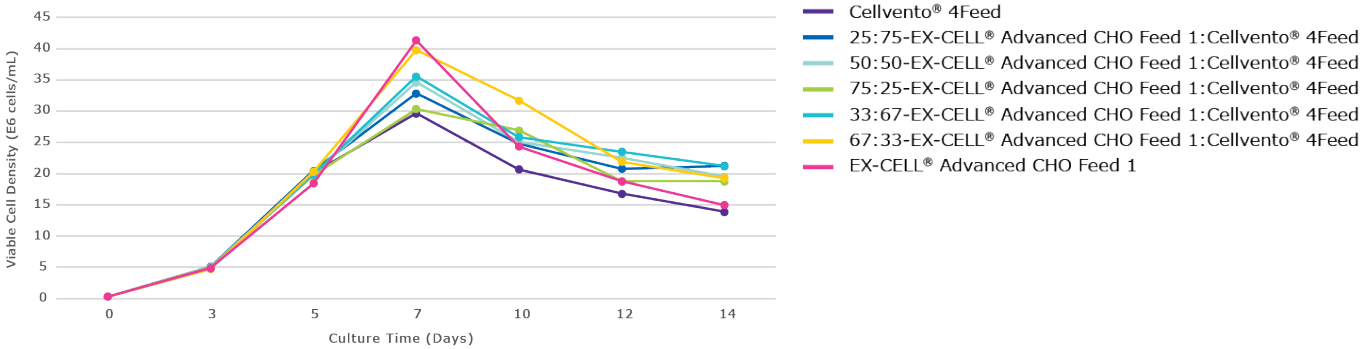

Figure 3A

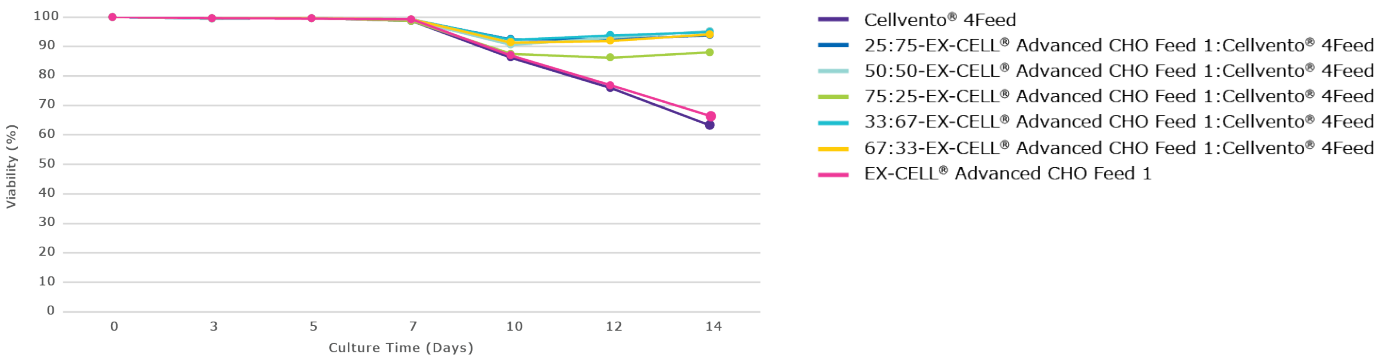

Figure 3B

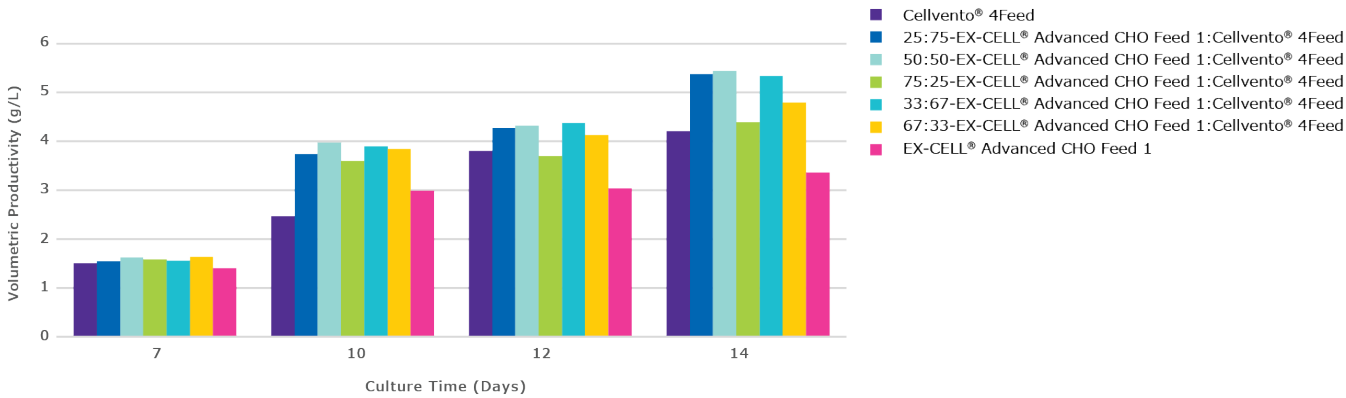

Figure 3C

Figure 3: Viable cell density (A), viability (B), and volumetric productivity (C) during the 14 day fed-batch process for CHOZN® mAb2 cultured in EX-CELL® Advanced CHO fed-batch medium.

CHOZN® mAb2 cultured in EX-CELL® Advanced CHO Fed-Batch Medium showed a preference for mixtures containing higher amounts of Cellvento® 4Feed. All mixtures containing at least 50% Cellvento® 4Feed showed equivalent peak volumetric productivity **(Figure 3C)**. Peak viable cell density varied by up to 9.5x10^6 cells/mL between mixtures **(Figure 3A)**. In contrast to Cellvento® 4Feed and EX-CELL® Advanced CHO Feed 1 alone, all mixtures maintained high viability throughout the fed-batch run **(Figure 3B)**. Cellvento® 4Feed, an important part of the high performing mixtures, experienced the lowest peak viable cell density when used alone and as such one of the lowest peak volumetric productivities. CHOZN® mAb2 cultured in Cellvento® 4CHO showed similar preferences with mixtures containing at least 67% Cellvento® 4Feed showing equivalent peak volumetric productivity (data not shown).

The results of this case study revealed a clonal preference in terms of the mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed. The impact of evaluating at least 75:25, 50:50 and 25:75 mixtures was observed, with CHOK1 mAb1 demonstrating the highest productivity when a 75:25 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed mixture was used and CHOZN® mAb2 when a 50:50 or 25:75 mixture was used. Regardless of whether EX-CELL® Advanced CHO Fed-Batch Medium or Cellvento® 4CHO was used, the CHOK1 mAb1 cell line preferred mixtures containing higher levels of EX-CELL® Advanced CHO Feed 1 while CHOZN® mAb2 preferred mixtures containing higher levels of Cellvento® 4Feed. In both cases, the preferred mixtures maintained viabilities above 85% throughout the 14 day process with peak viable cell densities on day 7 of between 20 and 35x10^6 cells/mL.

Study 3: Evaluating the scalability of a 50:50 mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed

In the third study, the high producing CHOZN® mAb2 cell line was grown using EX-CELL® Advanced CHO Fed-Batch Medium in a Mobius® 50L single-use bioreactor (Table 6). Scalability of a 50:50 mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed was confirmed using one of the highest producing fed-batch conditions for CHOZN® mAb2 determined in study 2.

Table 6: Experimental conditions and operating parameters used in Study 3

Experimental Condition	Operating Parameter
Culture Vessel	Mobius® 50L Single-Use Bioreactor
Initial Working Volume	35.86 L
Inoculation Density	5 x 10^5 viable cells/mL
Agitation	~ 14 W/m^3
DO setpoint	50%
Sparging strategy	O_2 through open pipe
pH set point/range	6.9 (+ 0.10 / - 0.15)
pH control	CO_2 and Na_2CO_3
Harvest Criterion	End culture after 13 days
Sampling Points	Study days 3,4,5,6,7,10,12,13
Sampling Volume	10-35 mL per day (depending on analysis needed)
Glucose Addition	On sample days, feeding to levels ≥ 6 g/L
Feed Schedule (50:50 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed)	5% Day 3, 5, 7.5% Day 7,10, 5% Day 12 (liquid feeds were mixed prior to administration)

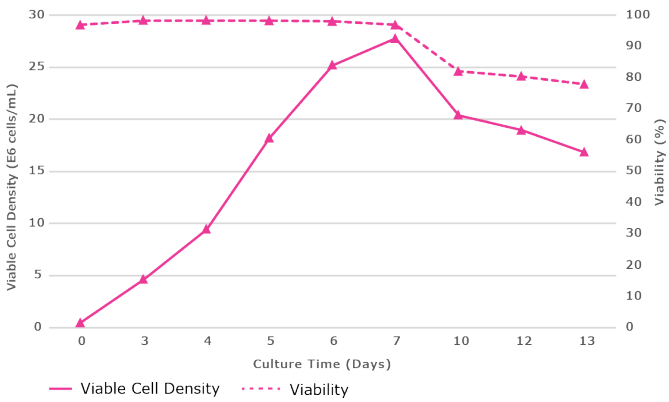

Figure 4A

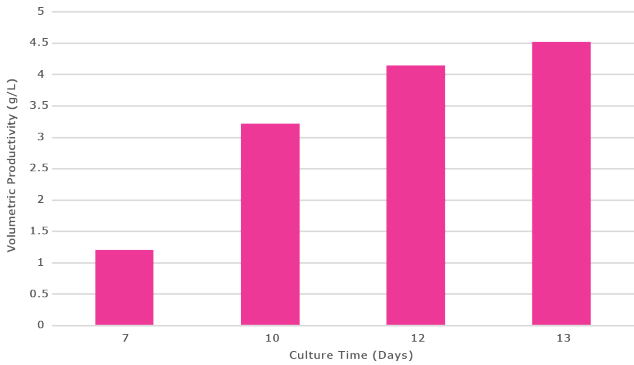

Figure 4B

Figure 4: (A) Viable cell density (solid line), viability (dashed line) and (B) volumetric productivity during the 13 Day fed-batch process for CHOZN® mAb2 cultured in a Mobius® 50L single-use bioreactor using EX-CELL® Advanced CHO fed batch medium fed 50:50 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed.

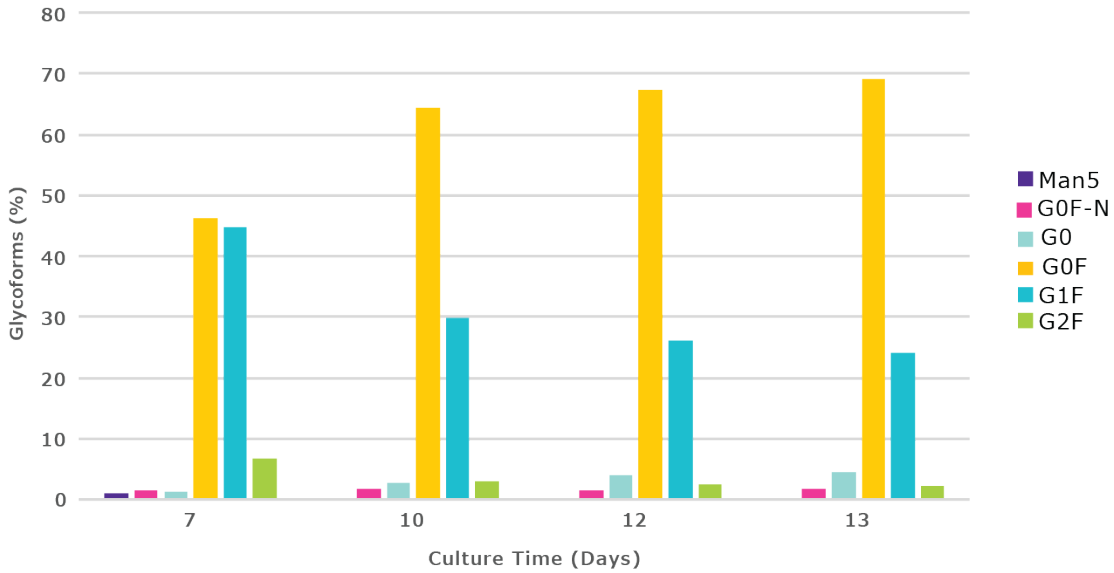

Figure 5: N-glycosylation profile during the 13 Day fed-batch process for CHOZN® mAb2 cultured in a Mobius® 50L single-use bioreactor using EX-CELL® Advanced CHO fed-batch medium fed 50:50 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed.

When cultured in a Mobius® 50L single-use bioreactor, CHOZN® mAb2 reached a peak viable cell density on day 7 of more than $27x10^6$ cells/mL with a viability over 96% **(Figure 4A)**. Volumetric productivity reached more than 4.5 g/L on day 13 **(Figure 4B)**. Comparable performance for the 50:50 EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed mixture was achieved in with spin tubes **(Figure 3C)** and a Mobius® 50L Single-use bioreactor **(Figure 4B)**. In the bioreactor, only subtle changes in the glycoprofile were observed following day 7. On day 13, this process yielded a high percentage of G0F, a significant percentage of G1F, less than 5% of G0F-N, G0, and G2F and no Man5 **(Figure 5).**

Conclusion:

While no single fed-batch system is applicable for all clones and situations, these case studies validate the approach of combining EX-CELL® Advanced and Cellvento® Fed-batch platforms to identify the optimum combination of medium and feed(s). Mixing and matching these products provides the opportunity to explore a more diverse range of cellular preferences in an efficient manner. A combination of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed in a variety of ratios showed promise for yielding the highest performance. A mixture of feeds, rather than a single feed, should therefore be considered if process performance is improved as shown in these case studies. Additional guidance for using the two feeds in combination can be found in "Cellvento® 4Feed and EX-CELL® Advanced Feed Mixing Protocol."

It is important to note that these medium and feed combinations may not be optimal for all cell lines. That said, these case studies represent what can be achieved through the use of the EX-CELL® Advanced and Cellvento® Fed-batch Platforms for these particular cell lines. Only through screening of various feed ratios, bolus volumes and timings can the optimal performance be achieved. It is possible that, even in these cases, additional performance could have been achieved through further manipulation of the feeding volume and timing alone or in combination with further variation of feed ratios. Complete optimization would require additional experimentation to fine-tune the fed-batch performance.

Performance is not always directly linked to total nutrients delivered. A subset of nutrients may be critical to a cell line and subsequently lead to seemingly unexpected improvements in performance. Cellvento® 4Feed fed at 18% total feed delivers a nearly equal amount of total nutrients as a 50:50 mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed fed at 30% total feed. If performance was exclusively based on delivering the most amount of nutrients in the least volume, then Cellvento® 4Feed would be expected to always deliver the best performance. In contrast, these studies demonstrate a mixture of EX-CELL® Advanced CHO Feed 1 and Cellvento® 4Feed fed at a higher total percentage is more beneficial for these cell lines. In this case, Cellvento® 4Feed delivers the highly concentrated source of key nutrients, such as amino acids, while EX-CELL® Advanced CHO Feed 1 delivers a less concentrated but more diverse source of nutrients.

As every cell line responds differently, an approach that evaluates feeds alone and in combination offers the best opportunity to maximize performance through delivery of the optimal mix of highly concentrated and diverse. A comprehensive evaluation of media and feeds can result in increased cell densities which support improved volumetric productivity and deliver important cost efficiencies.

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