

Total Cost-in-Use Analysis of a Chemically Defined Media Supplement, as Compared to a Legacy Process Using Peptone Supplementation

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ABSTRACT

Peptones have a long history of use as supplements in mammalian cell culture applications for biopharmaceutical drug production. However, biopharmaceutical manufacturers have increasingly focused on the identification of chemically defined alternatives to mitigate risk and improve consistency in their production processes. The risk reduction benefits of a chemically defined process are typically well characterized, but the total cost-in-use implications are less well understood.

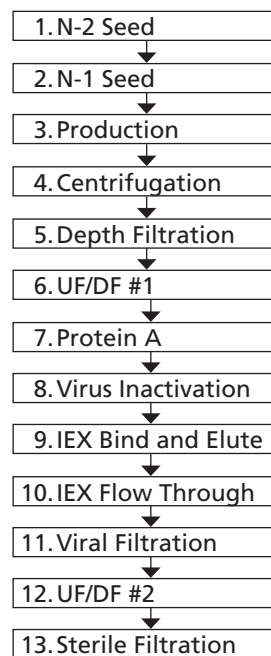
Using proprietary chemical separation and analysis methods on peptones has enabled BD to gain a greater understanding of the functional components; this knowledge has enabled the formulation of a new chemically-defined (CD) cell culture supplement, BD Recharge™.

BD has assessed the total cost-in-use implications of using a CD supplement – as compared to a legacy process using peptone supplementation – through a comprehensive manufacturing cost analysis using BioSolve™ software from BioPharm Services, Buckinghamshire, UK. Based on this assessment, the use of a CD supplement can deliver a significant reduction in total cost-of-goods by improving process reproducibility throughout upstream and downstream bioprocessing.

MATERIALS & METHODS

BD Biosciences – Advanced Bioprocessing conducted the cost-in-use analysis using Biosolve software licensed from BioPharm Services. For the purposes of this comparison, a 10,000L process in traditional stainless steel bioreactor systems was modelled. The process flow (Figure 1) shows the key manufacturing steps included in the analysis and is based on a representative monoclonal antibody manufacturing process. Except where noted, the cost-in-use analysis used industry average values, as determined by BioPharm Services in consultation with leading biopharmaceutical companies.

Figure 1. Process steps included in the model used to calculate cost of goods



MATERIALS & METHODS CONTINUED

To assess the total cost-in-use implications, the following parameters were assessed for both the legacy and new chemically defined process:

Material usage: For the legacy yeast extract peptone process, supplementation was 10g/L inclusive of base media concentration plus additional feed strategies. For BD Recharge, 50% of this amount or 5g/L was assumed based on the recommended usage protocols for the product, inclusive of base media concentration plus additional feed strategies.

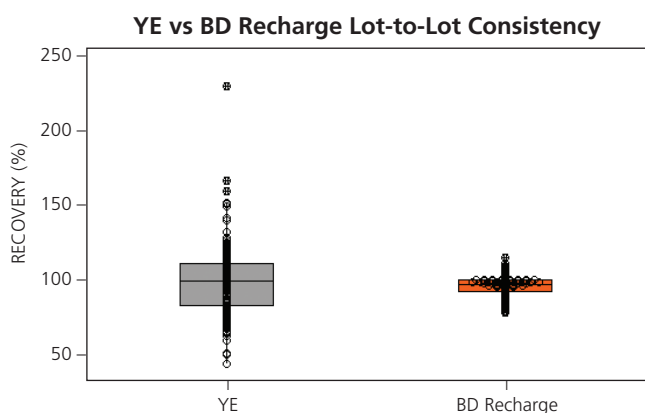
Material costs: List pricing was assumed as follows – BD Yeast Extract Peptone: \$200/kg, BD Recharge: \$1400/kg.

Batch failure rate: The average industry batch failure rate of 7.6% for >1000L batches^[1] was assumed for the legacy peptone process. Within this total, there were multiple causes of batch failure associated with undefined materials, including contamination (2.3%), material failure (0.6%), and failure to meet specs (1.0%).^[1] Chemically defined supplements may reduce failure rates, and in this analysis, a 40% reduction for these categories was assessed. For the chemically defined process, this represents a 1.6% overall reduction in the batch failure rate to 6.0%.

Upstream Yield / Titer: For the legacy yeast extract peptone process, a production titer of 5.0g/L was modelled. BD Recharge typically achieves comparable or greater protein yield compared to a yeast extract peptone. Accordingly, two scenarios were assessed for the chemically defined process: a) 100% yield or 5.0g/L, and b) 120% yield or 6.0g/L. Recognizing that yield performance is cell line dependant, a third scenario was also evaluated: c) 80% or 4.0g/L.

Efficiency: Since BD Recharge is a chemically defined formulation containing no components of molecular weight >500 Da, it is considered likely that there will be fewer column interactions. We chose to model this through decreasing the number of protein A reuses for peptone containing processes to 100 from Biosolve's standard value of 200 reuses.

Consistency: As a chemically defined formulation, the BD Recharge supplement is subject to far greater lot-to-lot component consistency than a yeast extract peptone, as shown by the following chart in which multiple lots of yeast extract (YE) and BD Recharge were analyzed by high-pressure liquid chromatography (HPLC) to measure the recovery of their components compared to input formulation.



Consistency in process raw materials can impact consistency in manufacturing processes. Accordingly, downstream purification operations are typically oversized relative to upstream operations by 25%^[2] in order to ensure that material from batches that outperform the mean can be captured and not lost as scrap. For the purposes of this evaluation it was assumed that a 25% increase in downstream purification capacity was required for a legacy peptone process and, that this oversizing could be reduced to 10% for a chemically defined supplement process.

MATERIALS & METHODS CONTINUED

Using the Biosolve software, the impact of batch-to-batch variability was assessed based on the required upstream and downstream equipment sizing to accommodate the maximum / minimum titers for a given targeted level of protein output.

The following table summarizes each of the scenarios assessed across these five parameters:

Table 1. Summary of input parameters used in subsequent modelling

| Parameter | Parameter Values | | | |
|--|------------------|--------------------------|--------------------------|--------------------------|
| | Peptone Process | BD Recharge Scenario "A" | BD Recharge Scenario "B" | BD Recharge Scenario "C" |
| Supplement Usage | 10g/L | 5g/L | 5g/L | 5g/L |
| Supplement Material Costs | \$200/kg | \$1400/kg | \$1400/kg | \$1400/kg |
| Batch Failure Rate | 7.6% | 6.0% | 6.0% | 6.0% |
| Protein A Resin Cycles | 100 | 200 | 200 | 200 |
| Downstream Purification Sizing vs. Upstream Operations | +25% | +10% | +10% | +10% |
| Relative Titer | 100% | 100% | 120% | 80% |

RESULTS

The parameters summarized in Table 1 were used as input parameters for the Biosolve software and the simulation was run. Figures 2-5 show the results generated by the model.

RESULTS CONTINUED

For each scenario, total cost of goods are summarized below:

Figure 2. Base Case – Yeast Extract Peptone Process

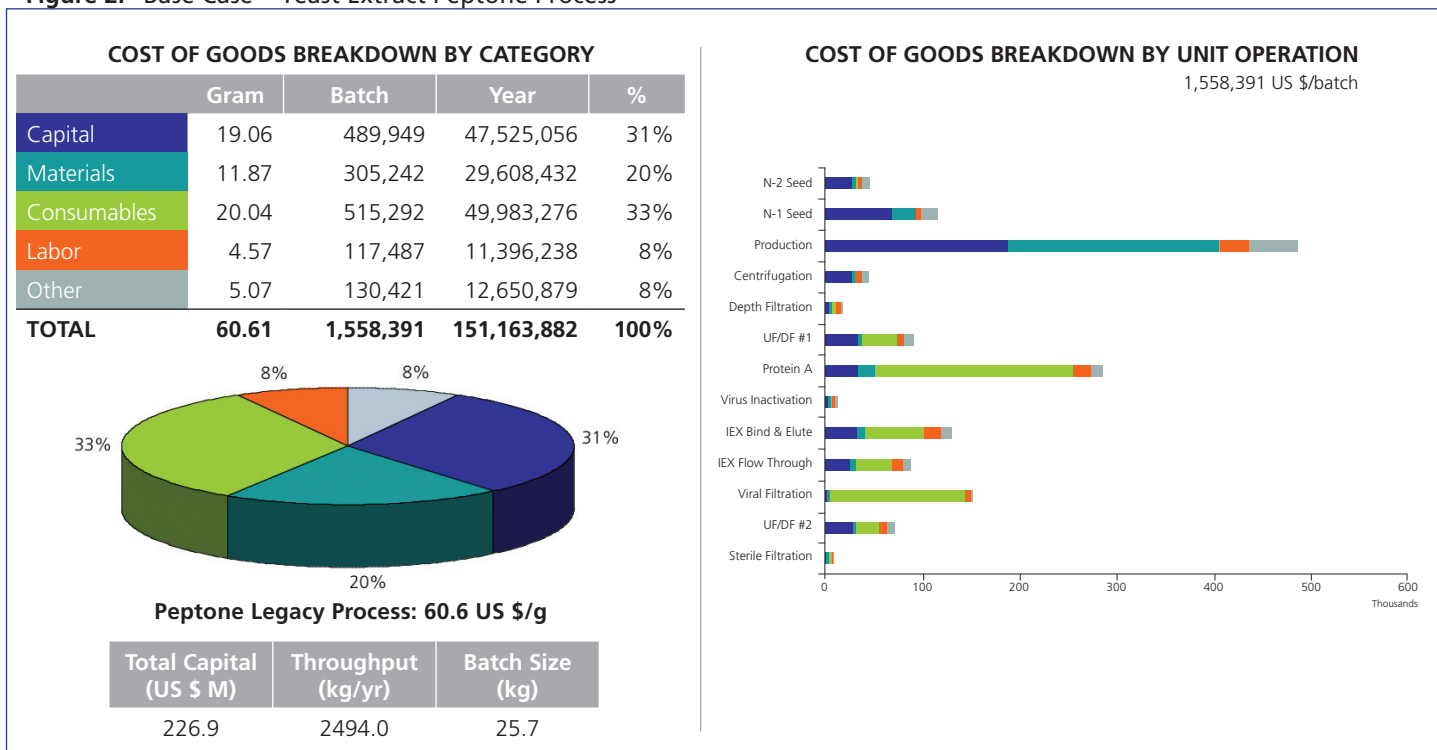
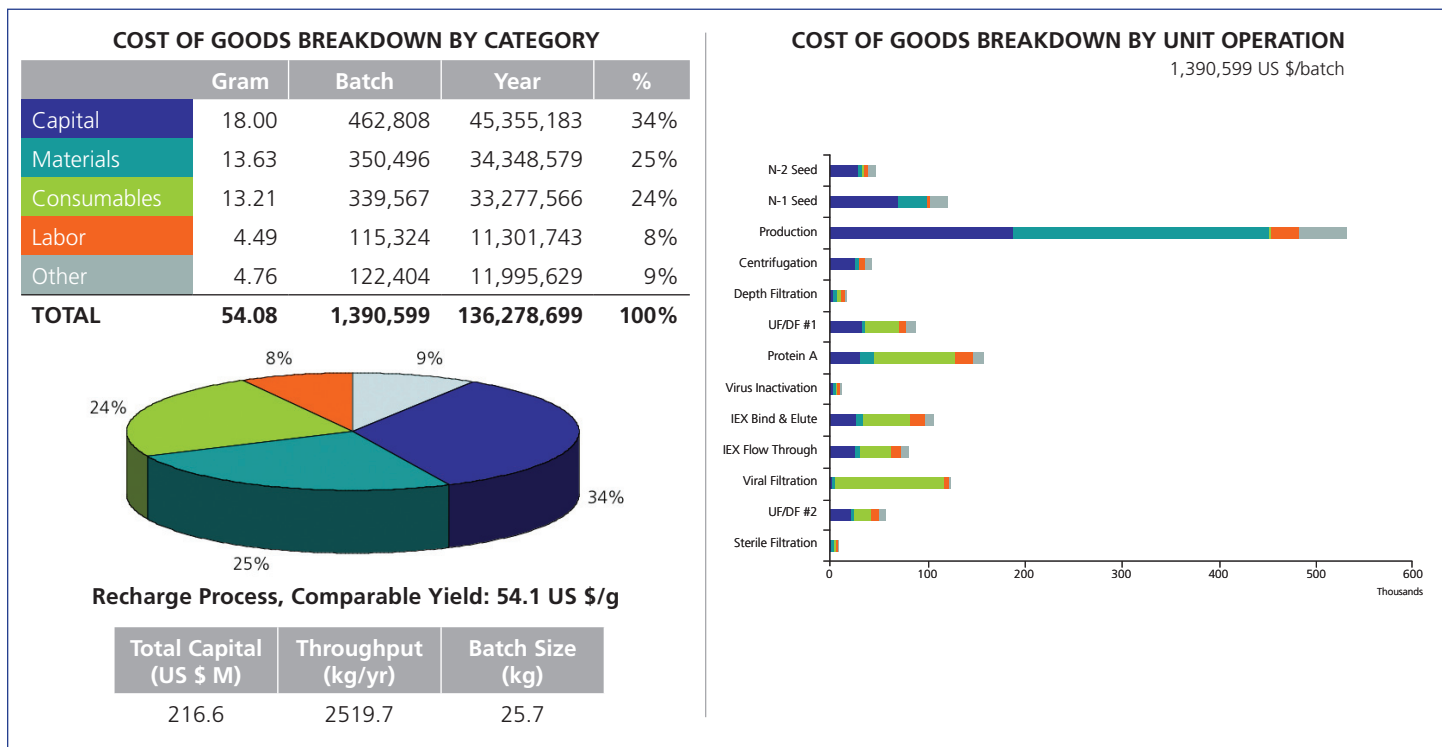


Figure 3. BD Recharge Scenario A



RESULTS CONTINUED

Figure 4. BD Recharge Scenario B

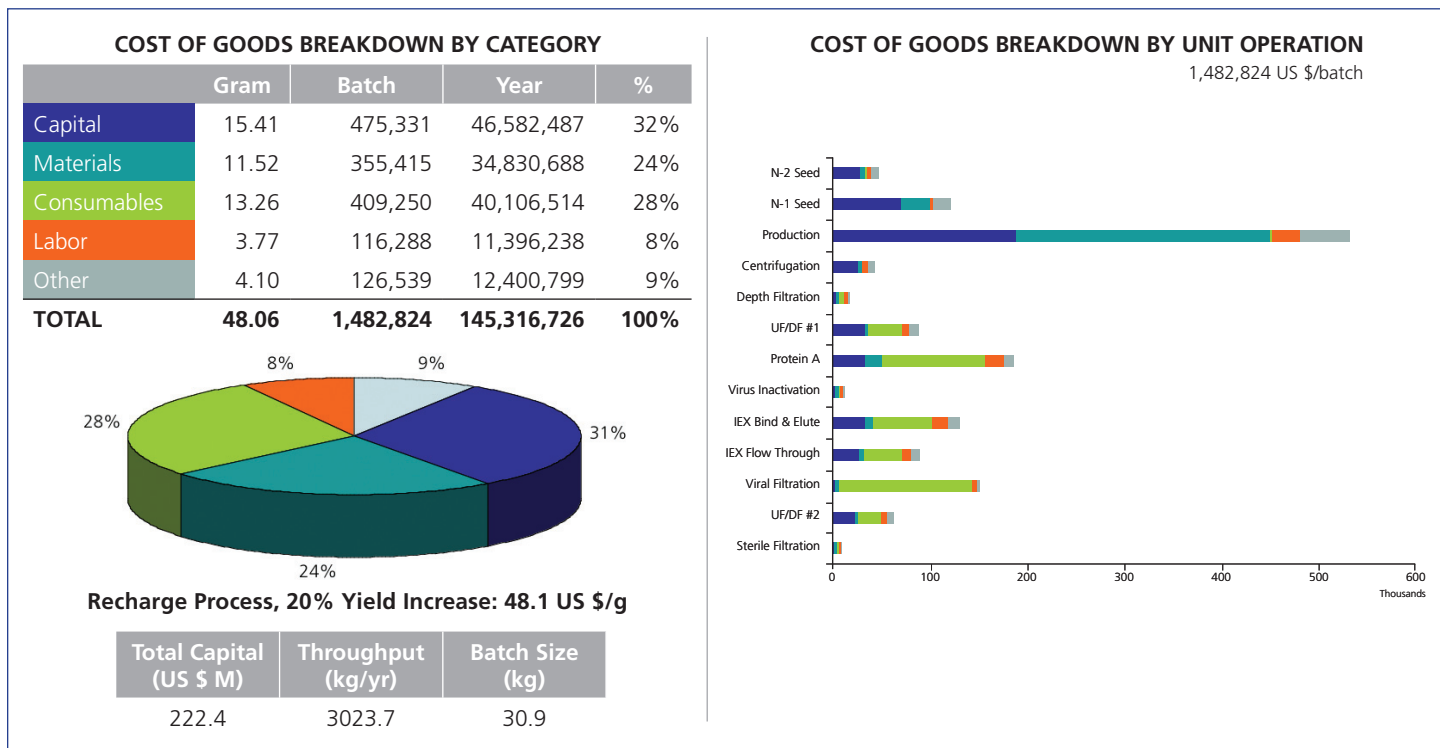
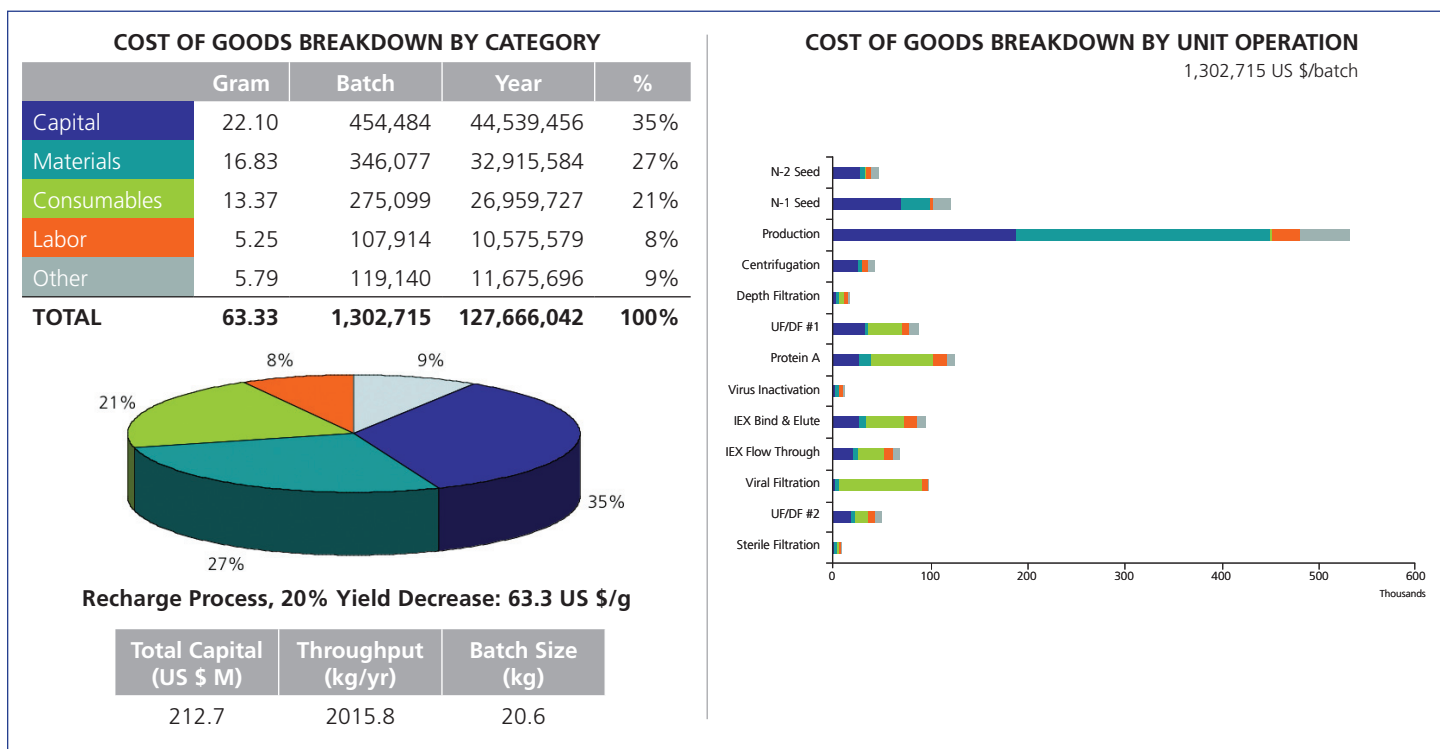


Figure 5. BD Recharge Scenario C



RESULTS CONTINUED

Using the BioSolve software, it was possible to investigate the cumulative effects of these changes on total manufacturing costs for each of the four scenarios. Total cost per gram of finished protein is summarized below.

Table 2. Summary of cost of goods (% change) for each scenario considered

| Scenario | Peptone Process | BD Recharge Scenario "A" | BD Recharge Scenario "B" | BD Recharge Scenario "C" |
|--|-----------------|--------------------------|--------------------------|--------------------------|
| Total Cost (\$ per gram of finished protein) | 60.6 | 54.1 (-11%) | 48.1 (-21%) | 63.3 (+4%) |

Despite slightly higher raw material costs, total manufacturing costs using a chemically defined supplement decreased by 11% as compared to the legacy yeast extract peptone process. For Scenario B, in which upstream process yields increased vs. the legacy process, total manufacturing costs decreased by 21%. Interestingly, for Scenario C in which upstream process yields decreased vs. the legacy process, the benefits of increased consistency offset the reduction in upstream titers, yielding a total manufacturing cost increase of only 4%.

OTHER BENEFITS

This analysis did not comprehend the following additional benefits of a chemically defined process:

- **Downstream Processing:** Since BD Recharge is protein free, downstream processing including column chromatography and other process steps may require less time and/or materials. While this aspect has to an extent been modelled by looking at resin reuse, there remain some potential additional benefits. For example, target protein capture may increase, or batch-to-batch cycle time may be reduced due to simplified cleaning requirements.
 - **Reduced Risk:** The elimination of undefined components significantly reduces risk of process related impurities and/or contamination associated with complex biologicals.
 - **Regulatory:** As a chemically defined, animal free, protein free supplement, BD Recharge is ultimately expected to reduce customers' regulatory burden.
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CONCLUSIONS

Use of the BioSolve software has allowed us to assess total manufacturing costs associated with a chemically defined supplement process, as compared to a legacy yeast extract peptone process. There are two conclusions:

- The improved process consistency associated with chemically defined processes can significantly lower total manufacturing costs.
- Adoption of a chemically defined supplement has only a minimal impact on total raw material costs.

BD Recharge is a chemically defined, animal free and protein free solution that offers improved raw material reproducibility and that typically achieves comparable or greater protein yield to a yeast extract peptone.

REFERENCES

1. Eric Langer, Biotech Facilities Average a Batch Failure Every 40.6 Weeks, *BioProcess International* 6(8), September 2008
2. BioPlan Associates, *Downstream Bioprocessing Panel Survey*, April 2011; unpublished
3. BioPharm Services UK, Lancer House, East Street, Chesham, Bucks HP5 1DG, United Kingdom

ACKNOWLEDGEMENTS

Biosolve is a trademark of BioPharm Services.

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