Platform process for production of monoclonal antibodies for research purposes – improvement option

Joern Meidahl Petersen1*, Claus Kristensen2

From 22nd European Society for Animal Cell Technology (ESACT) Meeting on Cell Based Technologies Vienna, Austria. 15-18 May 2011

Background
In 2006 Novo Nordisk decided to invest in building a pipeline within inflammatory disease management. To support this strategy the cell culture units had to establish technology for expression and production of monoclonal antibodies in CHO cells. A number of technology providers at that time offered proven platform processes for this purpose. It was decided to in-license one of these technology platforms, the one developed at Lonza Biologics, and focus research resources on product innovation rather than development of an in-house production system. The platform has now been fully implemented and the work flow optimised and standardised.

Platform process review
The platform process comprises:
- Host cell line/expression system
- Medium/feeds (chemically defined – animal derived component free)
- Process parameters
- Scale-down model (shake flask, 100 ml working volume).

The platform process has been applied for cell line development and antibody production for R&D purposes for five years. During this period 11 monoclonal antibodies have been transferred from laboratory scale to pilot plant production. The performance of the process platform across projects has been reviewed. The scope of the review was to compare yields obtained in the scale down model and yields obtained in the bioreactor process for all 11 antibodies. Figure 1 shows the results of the review.

In conclusion the review show that
- The cell lines are yielding 1.9 – 4.5 g/l mAb.
- The scale down model is predictive for the bioreactor process.

Evaluation of an improvement option
An upgrade of the medium, feeds and process protocols was offered by Lonza Biologics. A β-version of the latest process from Lonza has been tested and compared to the previous version in a study including five cell lines. The experiments were carried out in 100 ml shaker flask and the scale down version of the process was applied. A comparison of the two fed batch procedures is shown below:

<table>
<thead>
<tr>
<th>Current version: Version 6</th>
<th>New version: Version 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium and feeds CD-ACF</td>
<td>Medium and feeds CD-ACF</td>
</tr>
<tr>
<td>Two feed solution</td>
<td>Five feed solutions</td>
</tr>
<tr>
<td>Feed rates based on</td>
<td>Feed rates based on</td>
</tr>
<tr>
<td>○ Viable Cell Density</td>
<td>○ Viable Cell Density</td>
</tr>
<tr>
<td>○ Residual glucose</td>
<td>○ Residual glucose</td>
</tr>
<tr>
<td>○ Time</td>
<td>○ Time</td>
</tr>
</tbody>
</table>

The results of the study are compiled in table 1. The comparison of the β-test of improved platform process and the current process showed:
- mAb yields improved 1.3 – 2.4 fold
- No change in integrated cell area

* Correspondence: jmp@novonordisk.com
1Biopharm Manufacturing Development, API Support, Gentofte, Denmark, DK-2820
Full list of author information is available at the end of the article

© 2011 Petersen and Kristensen; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Improved lactate control may be the key to the yield improvement.

Acknowledgements
The following people all contributed with cell lines, data and/or stimulating discussions:
Lonza Biologics: Alison Porter, Jeetendra Vaghjiani.

Author details
1 Biopharm Manufacturing Development, API Support, Gentofte, Denmark, DK-2820. 2 Biopharmaceutical Research, Mammalian Cell Technology, Maaloev, Denmark, DK-2760.

Published: 22 November 2011

Table 1 Result of the comparison of the two versions of the fed batch process.

<table>
<thead>
<tr>
<th>mAb</th>
<th>Current version: Version 6</th>
<th>New version: Version 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICA (10E6 viable cell days/ml)</td>
<td>Lactate (mmol/l)</td>
</tr>
<tr>
<td>C</td>
<td>108</td>
<td>57</td>
</tr>
<tr>
<td>D</td>
<td>103</td>
<td>61</td>
</tr>
<tr>
<td>E</td>
<td>162</td>
<td>65</td>
</tr>
<tr>
<td>H</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>J</td>
<td>148</td>
<td>62</td>
</tr>
</tbody>
</table>

*ICA: Integrated Cell Area.

Figure 1 Yields of 11 antibodies in shake flask and bioreactors.

Submit your next manuscript to BioMed Central and take full advantage of:
- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit