5-6-2018

The journey from tech transfer to BLA submission: Case study of a NS0 cell culture process from 2000L stainless steel bioreactor to 2000L disposable bioreactor

Jincai Li
WuXi Biologics, China, li_jincai@wuxiapptec.com

Follow this and additional works at: http://dc.engconfintl.org/ccexvi

Part of the Engineering Commons

Recommended Citation

This Abstract and Presentation is brought to you for free and open access by the Proceedings at ECI Digital Archives. It has been accepted for inclusion in Cell Culture Engineering XVI by an authorized administrator of ECI Digital Archives. For more information, please contact franco@bepress.com.
The journey from tech transfer to BLA submission: case study of a NS0 cell culture process from 2000L Stainless steel bioreactor to 2000L disposable bioreactor

Jincai Li, PhD

Drug Substance Manufacturing (MFG1), WuXi Biologics, Wuxi, China. (li_jincai@wuxiappotec.com) Cell Culture Engineering XVI, Tampa, FL, May 6-11, 2018

Abstract

A case study of NS0 cell culture process transfer from 2000L stainless steel bioreactor (SST) to 2000L disposable bioreactor (SUB), and through to process validation and BLA submission is reported for production of an antibody therapeutics in this poster. Initial attempts in growing the NS0 cells in the small scale 2D bags yielded non-satisfactory results, as growth was impacted by bag material type as well as by different suppliers of the same bag material type. However, 3D bags of 50L and above proved to be supportive of the NS0 cell line growth.

Process characterization (PC) and process validation (PV) efforts were initiated after successful scale up to the 2000L SUB. Scale down model (3L) was qualified using bench top glass bioreactors, and PC studies identified several critical process parameters (CPPs). Successful process performance qualification (PPQ) campaign followed and BLA was submitted in 2017.

Leachables & extractables on SUBs

- Concern on L&E for cell culture is one of the main challenges for SUB implementation
- Impact of L&E for cell culture
  - Patient safety: toxic effects on patients
  - Process impact: cell culture performance impacts
- Not all bags are the same
  - Different bag have different materials & are made with different processes
  - Even bags with same contact layer material had different impact on growth
  - Other materials, e.g., additives, could have major impact
  - Ex: Thermo’s Aegis 5-14 film vs CX 5-14
- Suppliers might switch films
  - Ex: Sartorius Flexsafe S80 film replacing earlier S40 film

Lack of good scale down models for SUBs

- None of the major suppliers of SUBs offer representative scale-down models of the large scale SUBs
- 50L SUBs appear to be the most appropriate models to represent 2000L scale. But it is too expensive to be an economical model. Surface/volume ratio worse than 2000L
- Benchtop glass bioreactors are still being widely used as scale-down models for large scale SUBs.
- However, leachables & extractables cannot be tested with glass bioreactors. Product quality impact from SUBs also can not be evaluated with glass bioreactors

Growth challenges in 2D bags during process transfer (from 2000L stainless steel bioreactor to 2000L SUBs)

- Background: NS0 cell line with chemically-defined medium
  - Medium contains insulin & cholesterole
  - Robust process demonstrated by 2000L SST GMP runs
- Objective: transfer & scale-up to 2000L SUB for Phil trials
- Challenges in growing NS0 cells in disposable bags

Successful scale-up to 2000L SUB

- Process confirmation at 250L SUB
  - 250L SUB as last step before scaling up to 2000L SUB
  - Process designed to mimic 2000L operation as much as possible
  - Good performance at 250L SUB, with full analytical comparability assessment
  - Cleared to scale-up to 2000L SUB
- Successful scale-up to 2000L SUB
  - Growth & productivity at 2000L SUB (eng run & GMP run) matched very well with historical GMP data

Scale down models for 2000L SUBs

- Unexpected challenge in glycosylation profiles
  - Satellite cultures of 2000L SUB had dramatic difference in glycosylation profiles
  - One matched 2000L SUB well
  - The other had significant differences
  - Other performance indicators were comparable, e.g., titer, growth etc.

- Unexpected challenge in scale-down model transfer
  - Significant differences in glycan profiles among different small scale cultures
  - Difference between 1L vs 3L model
  - Even among 3L bioreactors, difference remained
  - Glass vessel had same dimensions
  - Agitator diameter different
  -ARGER different
  - Baffle presence or not also made a difference
  - Need to be careful in picking the right scale-down model!

Successful scale down model verification

- Picked the BR model that’s closest to 2000L SUB data, and also most consistent product quality data

Process Characterization & PPQ campaign

- Continuation of CPPs and obtaining design space with DoE studies
- Establishment of PAR & MAR with companion studies
- Scale down model qualification based on GMP scale for PC studies
- Identification of GQA that impact product safety and efficacy
- Four CPPs identified: N-1 culture & production culture medium concentration; culture temp; culture pH; 1st feed glucose & VCC level
- NOR (normal operation range) of the CPPs defined through DoE studies; MOR (max operation range) defined through univariate studies
- Control strategies defined based on development & PC studies

ACKNOWLEDGMENTS

- The author would like to thank members of the project team, the process development group, manufacturing organizations at WuXi Biologics for the contributions
- We would like also to thank the client for the collaborations