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Scale-up in the single use age: Does geometry matter?

Colin Jaques
Lonza Biologics, colin.jaques@lonza.com

Anthony Beaney
Lonza Biologics

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Colin Jaques, Lonza Biologics
colin.jaques@lonza.com
Anthony Beaney, Lonza Biologics

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Singe use bioreactors (SUBs) are becoming standard work horses in the biopharmaceutical industry. These SUBs are supplied by vendors as off the shelf designs limiting the cell culture engineer's ability to match the geometry of the SUB to the geometry of their existing stirred tank reactor (STR) capacity. The first generation of SUBs departed from conventional stirred tank bioreactor (STR) geometry in terms of impeller number, and orientation and sparger hole diameter. Moreover, one marked feature of SUB bioreactors was that they could be operated at lower volumes than conventional STRs, bringing considerable operational flexibility. This practice, however, further negated the principle of geometric similarity. This presentation considers the implications of changing reactor geometry on scale up of mammalian cell culture processes using multivariate data analysis to compare different geometries and different fill volumes. This approach uncovered a surprising result when working at half volume, which may not have been spotted using conventional data analysis methods.

The first generation of SUBs challenged two of the industry's key principles of scale up: geometric similarity and maintenance of K_La. As an early adopter of SUBs Lonza had to overcome these challenges. This was done by following an approach advocated by the SUB manufactures which departs from a conventional scale up strategy. Conditions were found empirically that matched the oxygen mass transfer in a conventional STR as closely as possible.

There is now however a wider variety of SUBs on the market, including vessels that display a higher degree of geometrical similarity to conventional STR geometry. As a result a study was performed to evaluate similarity of process performance between systems with different geometries in order to support Lonza's expansion of single use upstream capacity. In this study we have compared performance of two SUB systems; one with a conventional STR geometry (SUB 1) and one with a non-conventional geometry (SUB 2).

Mass transfer studies were performed with both systems using the gassing-out approach. Results demonstrated that empirical models built to describe K_La performance in Lonza's conventional STRs (10 to 20,000 L) were better able to predict K_La's in SUB 1 than in SUB 2, as would be expected given the geometries.

Cell culture evaluations were performed with a model cell line in both SUB systems. Multivariate analysis of the data showed that the behavior of the cultures performed in the SUB 1 was closer to behavior of cultures performed in Lonza's conventional scale-down model than those performed in SUB 2. However, Hoteling's T^2 and Q residuals analysis suggested that difference in behavior in SUB 2 was not extreme.

The impact of operating SUB 1 at half volume was investigated for two different vessel volumes. Multivariate data analysis showed that there was considerable difference in behavior of the cultures performed at half volume when compared to cultures performed in the conventional scale-down model. At several time points towards the end of the cultures, Q residual values were outside the 95% confidence interval, indicating significantly different culture behavior. Furthermore, the analysis indicated that there was also a difference in behavior of the half-volume cultures in different size vessels. This indicated a lack of scalability between half-volume cultures performed in different scale vessels of SUB 1, which was not apparent when the same vessels were run at full volume.

It was concluded that SUB geometry does matter when scaling processes up and should be a key consideration in a quality by design approach to minimizing differences in culture behavior during cell culture process scale up. Moreover, multivariate data analysis can provide useful supplemental insight in bioreactor process performance comparisons.