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# Single-use micro scale bioreactor enables higher productivity

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**Single-use micro scale bioreactor enables higher productivity**



Worldwide sales of biologic drugs including monoclonal antibodies (mAbs), fusion proteins and therapeutic enzymes now exceeds $120 billion per year. These therapies cost more than small molecules, in part because they are more expensive to manufacture. A strategy for reducing manufacturing COGs (cost of goods) is to use advanced automated micro and mini bioreactor models to improve upstream cell culture productivity by selecting better clones and enabling more efficient optimisation of media, feed and culture conditions.

Traditionally, cell culture development for bioprocessing begins with screening to find clones that express the most protein. This is usually performed in small volumes of 0.1mL to 6mL using a multiwell plate format. Because of the need to conduct large numbers of experiments this has resulted in the development of systems based on 24 well single-use multiwell plate. These have the advantage of being quick and easy to set up and use and because the multiwell plate are pre-sterilised there is no pre-process preparation and as they are single-use there is no post-run cleaning. Some of these multiwell plate systems do provide monitoring and some control of dissolved oxygen (DO) and pH but have the drawback that they do not mimic the sparging or stirring action of a large scale bioreactor as they rely on shaking for mixing. Additionally, they do not provide automated feeding and have a working volume of less than 6mL, which limits the amount of analytical testing possible.

Clone selection and early process development to identify the most productive clones and define optimal media or culture conditions is typically performed in shake flasks with two or three top clones carried forward for evaluation in bench top bioreactors. Using shake flasks and bench top bioreactors is very labour intensive and as they are generally made of glass, require time consuming pre and post-process cleaning and sterilisation for every experimental run.

Shake flasks provide no active control of pH and DO, relying on the buffering capacity of the media and the gas environment of the incubator. The mixing environment is unlike that in a bioreactor as there is no impeller. Additionally, shake flasks are often manipulated by hand, making it difficult to perform nutrient feeding or sampling without introducing variability. Hence, the use of shake flasks can often result in different cell growth and titre profiles to those seen after scale-up in a bioreactor. Data published in Cytology of a study at Genentech demonstrates that when cultured in shake flasks, Chinese Hamster Ovary (CHO) clones expressing mAbs do not show comparable culture performance with those grown in 2L bench top bioreactors.

Using bench top bioreactors does mimic the sparging and stirring action of a large scale bioreactor but they require considerable amounts of time for set-up, operation and post-experimental cleaning and sterilisation. Therefore, the amount of available resource often limits use of bench top bioreactors requiring that researchers have to select only their top clones to test in this way. This can lead to the final choice of clone sometimes performing sub-optimally upon scale-up, adversely affecting yield and titre. If a larger number of runs could be performed during clone selection under conditions which are representative of the scale-up bioreactor environment, then it should be possible to isolate a better performing clone for use in manufacturing and potentially save thousands of dollars in manufacturing COGs.

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To meet the need for a single-use bioreactor model that provides comparable mixing, gassing and sampling parameters to be used in place of shake flasks and bench top bioreactors, the advanced micro and mini scale bioreactor systems, ambr15 and ambr250 (Sartorius-Stedim Biotech) have been developed. These integrated systems combine 10-15mL or 100-250mL single-use bioreactor, with an automated liquid handling workstation and dedicated control and analysis software. Critical to the use of these systems as bioreactor models is the geometric similarity to larger bioreactors and that their contents are stirred by an impeller and gases can be supplied by sparging. In addition, the software control systems and integrated single use sensors enable these systems to control the culture conditions in a similar way to large scale systems ensuring scalability.

Each workstation maintains aseptic conditions using a HEPPA filtered environment (ambr 15 can be installed in a standard biological safety cabinet and the ambr 250 includes an integrated system) and provides independent parallel control of either 12 or 24 (ambr 250), 24 or 48 (ambr 15) bioreactors. The workstation controls the stir speed, gas supply and temperature and also provides liquid handling automation functions for the bioreactors, each of which can have its own medium, feed, inoculum and sampling strategy. Each bioreactor also incorporates sensors for real-time measurement and bioreactor-specific automated control of DO and pH and set points.

A major contract research organisation (CRO) compared the timelines for clone selection and early process development of a mAb expressing (CHO) clone using shake flasks and bench top bioreactors with the automated micro bioreactor. The results showed that with reusable shake flasks and bench top bioreactors, clone selection and early process development took around 22 weeks, whereas using the single-use micro bioreactors and a confirmatory run in a reusable bench top bioreactor this was reduced to six weeks.

Single-use micro and mini bioreactor technology can provide an accurate prediction of cell growth and protein titre achieved in bench top bioreactors. Setting up and running reusable shake flasks and bench top bioreactors is manually intensive, while the fully automated single-use micro and mini bioreactor is more convenient, taking much less time to set-up and run, as well as requiring no time consuming post run cleaning and sterilizing. Thus clone selection and early process development can be performed rapidly and efficiently, increasing the number of clones that can be evaluated by up to ten fold. This improves the chances of selecting a clone with optimal growth and protein expression. The automated system makes it easy to implement DoE into the work flow and the geometric similarity of the platforms reduces the risks for scale-up to larger single-use pilot and manufacturing scale stirred bioreactors, reducing time-lines and saving cost.
Author

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