Optimize Clone Screening: Time Savings with the Cydem VT System in Monoclonal Antibody-Producing Cell Line Development Workflows

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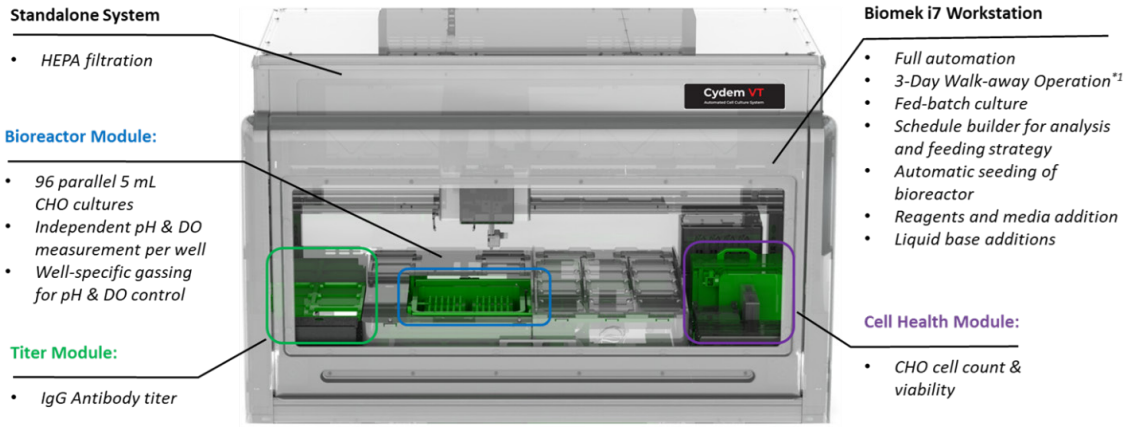
Introduction

Since the first monoclonal antibody (*mAb*) used to prevent kidney rejection was fully licensed in 1986 (1), commercially sponsored monoclonal antibody therapeutics development continues to grow into 2024 with nearly fifty candidates under consideration for regulatory review and approval success rates ranging from 14-32% (2). With a predicted compound annual growth rate (CAGR) of approximately 11 % from 2024 to 2033 (3), an efficient development process to drive *mAbs* to market smoothly is essential. More importantly, the recent COVID-19 pandemic highlights the importance of a rapid *mAbs* development process to bring life-saving medications to patients as expeditiously as possible.

As the field moves away from animal-based hybridoma production techniques and scales up with culture-based methods using hosts such as Chinese hamster ovarian (CHO) cells, technological advancements become increasingly important to improve yields and reduce costs. One method of reducing costs is by performing high throughput screening (HTS) of antibody-producing clones using miniaturized bioreactors. Various platforms (4) have been developed using a multi-instrument infrastructure to incorporate cell culture and analytical devices to monitor critical process parameters (CPP) and critical quality attributes (CQA). For example, an automated liquid handler may have an incorporated robot arm that can access microtiter plates from an incubator to draw samples and deliver them to various integrated analytical devices, or to a vessel which may be delivered manually to an unintegrated device. After analysis, data can be pulled from the various devices and processed by researchers to ultimately gain insight into which clones are top performers. This type of cell line development process can be cumbersome and requires an in-depth understanding of each analytical device in addition to specialized automation integration knowledge to successfully combine them into a functional system. Frequently, these instruments are produced by different manufacturers and come with varying levels of maintenance plans and support, adding an extra layer of complexity to their upkeep.

The Cydem VT Automated Clone Screening System, by Beckman Coulter Life Sciences, is a standalone system comprised of a liquid handler with integrated incubation, antibody titer, and cell health modules which allows parallel cultivation of 96 microbioreactors in controlled fed-batch conditions with well-specific gas and pH adjustment and on-deck measurement of cell count, viability and antibody titers. Gases and bases are automatically delivered to individual wells based on user-defined pH and dissolved oxygen (DO) setpoints. Feeds, additives, and base addition times can be scheduled or added on demand. The unified data structure enables analysis of a single, intuitively formatted export file. To highlight the efficiency benefits unlocked by the Cydem VT Automated Clone Screening System, the time to maintain a 14-day fed batch clone screening experiment was estimated and compared against manual methods using shaker flasks and 24 deep well plates.



*1 Campaigns can run longer but reagents do not need to be refilled more often than every three days

Figure 1: Cydem VT system components. The Cydem VT Automated Clone Screening System includes a bioreactor module plus antibody titer and cell health analytical modules integrated into a Biomek i7 workstation.

Methodology:

Time savings calculations were based on full-time employee (FTE) hour estimates for a 14-day fed-batch experiment. Time estimates were based on the addition of three feeds plus cell heath and antibody tests (Table 1). Offline antibody titer tests (shaker flasks and deep well plates) were estimated based on the Cedex Bio HT bioanalyzer (Roche). Offline cell counts and viability analyses, for the shaker flasks and 24 deep well plates, were estimated based on the Vi-CELL BLU cell viability analyzer (Beckman Coulter Life Sciences).

Day	Feed 1	Feed 2	Feed 3	Cell Health	Titer
1				✓	
2-3					
4	✓	✓	✓	✓	✓
5	✓	✓	✓	✓	
6	✓	✓	✓	✓	✓
7	✓	✓	✓	✓	
8	✓	✓	✓	✓	✓
9	✓	✓	✓	✓	
10-14	✓	✓	✓	✓	✓

Table 1: Activity schedule for time estimates. Feed additions were scheduled for 11/14 days. Cell health tests were scheduled for 12/14 days. Antibody titer tests were scheduled for 8/14 days.

Results:

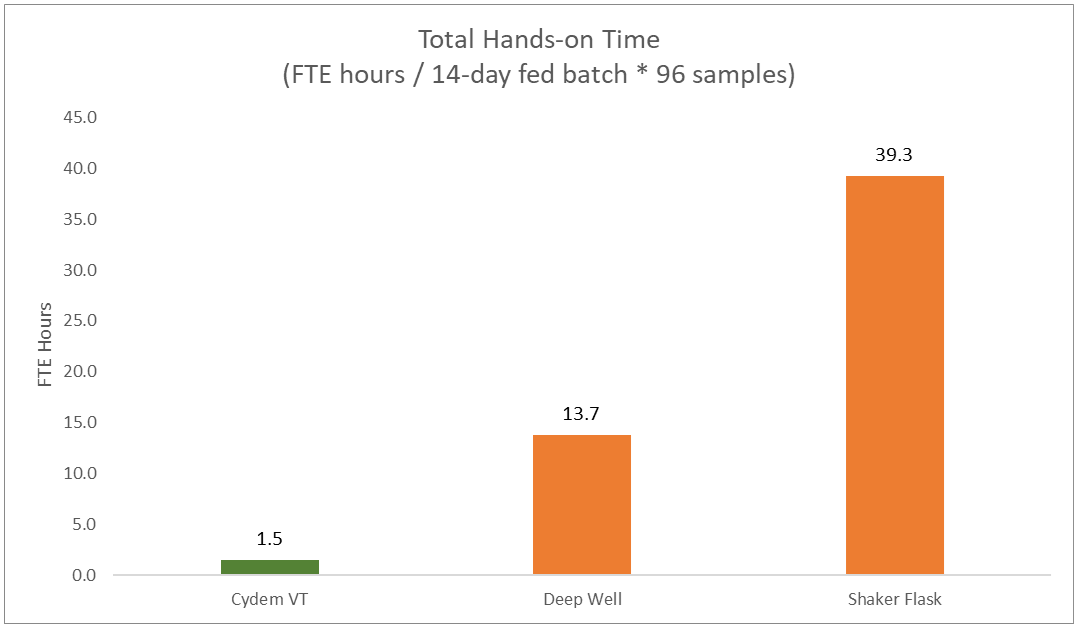


Figure 2: Total hands-on time was estimated based on an automated Cydem VT Automated Clone Screening System 4x24 microbioreactor workflow and two manual workflows for 4x24 deep well plates and 96x250 mL capacity shaker flasks. The Cedex Bio HT bioanalyzer and Vi-CELL BLU viability analyzer were considered for offline titer and cell health estimates, respectively. Experiment startup and shut down times were not included.

Conclusions:

Based on the estimations above, the Cydem VT screening system is predicted to provide up to 26 times the hands-on time savings compared to manual fed-batch screening experiments. This allows highly trained specialists to allocate their time to additional experiments or focus on activities such as data analysis and report writing.

Automating the screening process offers numerous benefits beyond just time savings. One significant advantage is maintaining cultures under controlled conditions for feeding and sampling, thanks to the temperature, gassing, and shaking speed-controlled bioreactor. In contrast, standard cultures are typically moved in and out of incubators, exposing them to uncontrolled conditions during sample collection. Automation eliminates operator errors such as forgetting to pipette feeds into wells, adding reagents to the wrong wells, or using incorrect volumes of additives. Analytical times and feed deliveries can be scheduled, ensuring consistent data comparison from day to day without the variability caused by delays. Additionally, automation reduces ergonomic risks for operators by decreasing the frequency of pipetting and the handling of large, cumbersome shaker flasks. There are also ecological benefits from reduced plastic waste, as the system uses reusable stainless-steel fixed tips for sampling and reagent delivery.

Aside from these hands-off benefits, the system enables frequent inline monitoring of pH, biomass, and dissolved oxygen (DO) under consistent, automation-driven conditions. The proportional-integral-derivative (PID) controller allows real-time adjustments for CO_2, N_2, and O_2 gassing without user intervention. Such monitoring is often not performed for shaker flask and deep well culture screening. Other benefits include a smaller footprint and comprehensive maintenance plans from a single vendor.

The Cydem VT Automated Clone Screening System empowers high demand scientists by freeing them from manual, labor-intensive clone screening processes, allowing them to explore innovative technologies and workflow improvements while maintaining automated, controlled microbioreactor conditions.

References:

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