

Overview

Cell cultivation is an essential process in the production of many therapeutic proteins, cell therapy, stem cell research, tissue engineering and high throughput, high content cell-based screening. Cell culture is a complex process consisting of multiple tasks, including cell seeding, growing, harvesting, counting and passaging. Many cell-based applications also require very time-consuming processes for formulation development, clone selection and evaluation to ensure reproducibility.

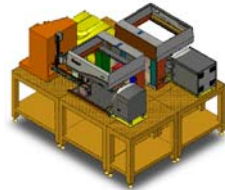
Because of the complexities of structures and physicochemical properties of antibodies and other therapeutic proteins, production cell lines and their culture media and processes must be optimized to ensure product quality and quantity. Processes may need to run for weeks or months under the demands of maintaining sterility and managing all relevant data information.

In this report, integrations of cellular analytical devices such as a viability analyzer, flow cytometer and multimode plate reader and cell culture incubators on automated liquid handling systems are described. Together with process and data management software, these modular integrated systems provide a flexible and expandable automation platform. When incorporated into cultivation processes, these systems provide functionality to streamline automated cell handling, including sample tracking and data management.

Introduction

- Cell cultivation
 - Antibody production
 - Therapeutic protein production
 - Vaccine production
 - Stem cell research
 - High content screening and cell based assays
 - Cell therapy and tissue engineering
- Challenges
 - Complexities of structure and physicochemical properties of antibodies and other therapeutic proteins
 - Time consuming process of formulation development, clone selection and evaluation
 - Requirements of Quality by Design (QbD) to define design and control spaces
 - Low throughput with shaker flasks
 - Replicates and variables for multi-factorial experimental designs
 - Continuous culturing and production of cells
 - Human errors and standardization
 - Sample tracking, data management and analysis

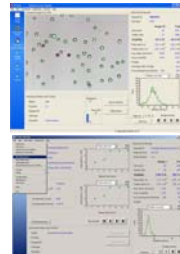
Integrated Cellular Analysis Devices and Incubators



- Integrated systems
 - Biomek NX[®] Span-8 with Biomek NX[®] Multichannel
 - Vi-CELL[®] XR with Biomek NX[®] Span-8
 - Quanta[™] SC MPL with Biomek NX[®] Span-8 via BRT Robotic Loader
 - PARADIGM[™] with Biomek NX[®] Multichannel
 - Cytomat[®] Hotel with Biomek NX[®] Span-8
 - INHECO Incubator Shaker MP with Biomek NX[®] Multichannel
 - INHECO Incubator MP with Biomek NX[®] Multichannel
- Flexible modular system for scale-down modeling
 - 50 mL tube
 - CELLSTAR AutoFlask^{*}
 - 6, 24, 48 or 96-well plates (standard or deep-well)
- Expandable
 - Easy expandability and integration with external devices
 - Other detectors or storage devices
 - Centrifuges
- BL I or II safety enclosure (available) to provide optimum protection for personnel, product, and the environment
- Integrated Vi-CELL XR



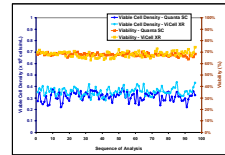
- Cell viability analyzer
- Measures total and viable cell density (VCD) and viability
- Measures cell size and distribution (3-70 μm)
- Calculates bioprocess growth rate
- Calculates bioprocess doubling time
- Comes with validated reagents



Integrated Quanta SC MPL

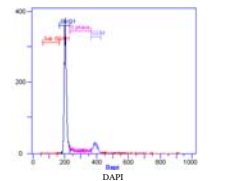


- High throughput, advanced flow cytometer with 3-color fluorescence, Coulter volume, side scatter and absolute count measurements
- Measures total and viable cell density (VCD) and viability
- Measures cell size
- Detects apoptosis
- Detects cell surface and intracellular proteins
- Analyzes cell cycle
- Comes with validated reagents

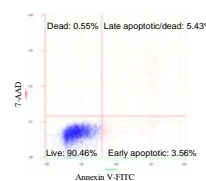


Cell count and viability measurements by Quanta SC MPL and Vi-CELL XR

(Cheung, Song, Shun, Beckman Coulter Cellular Research Newsletter, Issue 3, 2007)

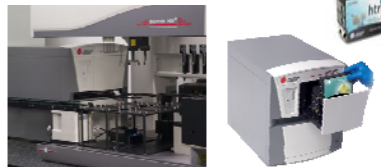


Cell cycle analysis with Nuclear Isolation Medium with 4',6'-diamidino-2-phenylindole (NIM-DAPI).

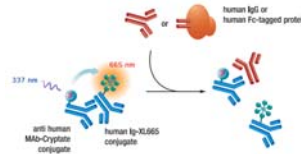


Apoptosis analysis with Annexin V-FITC and 7-aminoactinomycin D (7-AAD)

Integrated PARADIGM



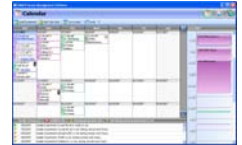
- Modular High Throughput Multimode Plate Reader
- Maximum flexibility for multiple applications
- Determines IgG concentration
- Measures pH and dissolved oxygen
- Measures glucose and lactate concentrations.



Cisbio Human IgG HTRF[®] assay

Software Support for Critical Tasks

- Enables users to run and monitor complex processes over weeks and months.
- Utilizes the integrated SQL data-base to ensure integrity of all process steps.
- Data Acquisition and Reporting tool (DART)
 - An integral part of the workstation
 - Ensures data integrity between tasks and utilizes the integrated SQL database
 - Allows tracking of locations for every single sample/plate in the system at any point of time.
- SAMI[®] Process Management Software
 - Organizes parallel and interleaved processes
 - Includes a calendar view of future, current and completed tasks within the system
 - Includes a view to simplify laboratory resource management
 - Provides easy access to more detailed reports
 - Provides flexibility for the user to optimize each single step within a process and configure entirely new processes.



Task Definition and Optimization
 SAMI EX optimizing scheduler defines and runs individual tasks in any cell cultivation process. New tasks can be developed on a simulation system without interfering with existing processes.



Planning and Process Definition and Optimization
 SAMI Process Definition Editor is an intuitive graphical user interface to map tasks within a complete process. Any SAMI EX task is available as a building block for new processes or process variations.

Automated Assay Optimization (AAO) for Process Development



- Allows use of design of experiment (DOE) for formulation development and optimization
- Allows seamless transfer from DOE design into Biomek method and data analysis
- Speeds up process development and transition to high throughput operation.

