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Advanced Bioprocess Development and Manufacturing Technologies in High-Throughput Miniature Bioreactors

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Abstract: In recent years, the importance of a rapid response to influenza pandemics has been widely recognized. However, traditional technologies for bioprocess development and manufacturing are unable to meet such a rapid response. Healthcare companies and related organizations in the United States, including the US Department of Health and Human Services, have proposed and initiated the development of a next-generation technology platform for advanced bioprocess development and manufacturing (ABDM). The goal of ABDM is to reduce the timeframe significantly for bioprocess development and manufacturing, enabling a prompt response to influenza pandemics and preventing them from spreading. Concurrently, developments in precision medicine have presented new demands for the biopharmaceutical industry. The small-scale production and fast turnaround time required in precision medicine have subsequently required an accelerated development and manufacturing timeframe. At the same time, the number of product subgroups will increase, and the batch sizes and final product amounts will decrease. To satisfy these production and turnaround time requirements, ABDM uses micro- and mini-bioreactors. Specifically, the major features of the ABDM technology platform include high-throughput screening and process development based on micro- and mini-bioreactors, disposable technologies, modular unit operations, and flexible manufacturing. The development of ABDM in China will directly strengthen national security, improve public welfare, and provide great social and economic value. The impact of this next-generation technology platform will spread throughout the entire biomanufacturing industry and mark a new era for bioprocess development and manufacturing.
Keywords: advanced bioprocess development and manufacturing; pandemics; precision medicine; mini-bioreactor; high-throughput technology; disposable technology; flexible manufacturing

1. Background of advanced bioprocess development and manufacturing

Major events that cause significant human casualties and deaths can greatly influence our lives and are occurring at an alarming rate. Such events can take several forms, including natural disasters (e.g., earthquakes and floods) and man-made tragedies (e.g., conflicts and wars), and have often received significant attention from news outlets and the public. However, during the past few decades, as science and advances in human health have become mainstream, the public has become more aware of other types of disasters such as disease pandemics that can also cause significant human casualties and deaths.

1.1. Risks and impacts of disease pandemics

Disease pandemics have routinely been shown to be just as costly and lethal as other types of major disasters. The outbreak

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of the H1N1 flu, which began in Spain and continued from January 1918 to December 1920, was one of the deadliest tragedies in modern human history. Within the first 25 weeks after the initial outbreak, the H1N1 flu caused the deaths of approximately 25 million people, exceeding the total death toll reached by the end of World War I. At its conclusion, over 500 million people were infected, of which, roughly 50 million to 100 million died [1].

Two of the major characteristics of a disease pandemic are its outbreak and unpredictability. According to the US Centers for Disease Control and Prevention (CDC), the Asian flu pandemic (H2N2) in 1957 caused 1 million to 4 million people globally to lose their lives —of them, 60 000 to 80 000 were Americans. The number of American lives lost to the H2N2 flu exceeded the total casualties of the Vietnam War. Similarly, in 1968, the Hong Kong flu (H3N2) resulted in the deaths of 1to 4 million people globally. The 30 000 Americans killed by the H3N2 flu was equivalent to the total casualties at the end of the Korean War. Even in the 21st century, disease pandemics are still frequent and just as significant. Notable outbreaks include the severe acute respiratory syndrome (SARS) in China from 2002–2003, the highly pathogenic avian influenza (H5N1) in 2004, the swine flu (H1N1) in 2009, the bird flu (H7N9) from 2013–2014 [2], and the most recent Ebola and Zika viruses.

Such disasters are often catastrophic to human civilization. However, these disasters and associated tragedies are fundamental catalysts for the advancements of science and technology. These advancements can accelerate the time required for both basic and applied research. To counter frequent disease pandemics, modern societies must focus on the weakest aspects of the healthcare and pharmaceutical industries related to prevention, diagnosis, drug development, and production. Similar to other types of disasters, timing is critical when encountering a disease pandemic.

1.2. Advanced bioprocess development and manufacturing in the United States

Spurred by the terrorist attacks on September 11, 2001 and the increase in incidents of bioterrorism that followed, the US government integrated bioterrorism threats into its national security strategy. The outbreak of the swine flu in 2009 further demonstrated the US government's technological limitations against chemical, biological, radiological, and nuclear (CBRN) threats and pandemic diseases including influenza. To effectively respond to such threats, measures akin to advanced bioprocess development and manufacturing (ABDM) are required.

According to the US Department of Health and Human Services (HHS), it typically takes 12 weeks between the onset of an influenza occurrence and the development of a pandemic [3]. If a corresponding vaccine can be developed and manufactured within this 12-week period and effectively administered to the public, the mortality rate and damage caused by the influenza could be greatly reduced. In a 2009 request for proposals, the US HHS stressed that advanced technologies that are able to promptly respond to the threats of influenza pandemics should be developed. One of the agency's targets was to develop and manufacture the first dose of the corresponding vaccine within 12 weeks of pandemic onset and deliver a surge capacity of 50 million doses within six months [4]. In 2009, the US HHS allocated 330 million US dollars to support the development of ABDM projects; it has since allocated more than 8 billion US dollars for ABDM, including 440 million US dollars in 2012 to establish three Centers for Innovation in Advanced Development and Manufacturing (CIADM) [3,5].

1.3. Advanced bioprocess development and manufacturing in precision medicine

In 2011, the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council published a major proposal titled, "Toward Precision Medicine." On January 30, 2015, US President Obama officially launched the Precision Medicine Project to push forward the development of individual and personalized medications [6,7]. Differing vastly from traditional medication production, the advancement of precision medicine can significantly improve disease prevention and the development of cures. This advancement, however, is not without challenges.

Many current treatments offer a one-size-fits-all approach, in which the same drug is administered to a large cohort of patients who have been diagnosed with a particular disease. Not all patients respond in the same way to the same type of treatment, and side effects often vary greatly from patient to patient. Precision medicine offers the ability to tailor a drug to meet a patient's specific needs and individual genetic factors. However, technological challenges regarding drug manufacturing and administration methods exist. The traditional high-yield, low-cost manufacturing process does not align with the principles of precision medicine. The small-scale production and fast turnaround time required in precision medicine subsequently require an accelerated development and manufacturing timeframe. At the same time, the number of product subgroups will increase, and the batch sizes and final product amounts will decrease. The advanced bioprocess development and manufacturing technology platform meets the requirements of multiple products, small-scale production, and flexible manufacturing. More importantly, the development and manufacturing times will be significantly reduced [8].

1.4. Motivation for advanced bioprocess development and manufacturing

In addition to disease pandemics, humans routinely face several other types of threats. A shortage of resources and envi-

ronmental pollution are two other important threats to modern civilization. An effective strategy for addressing the challenges of energy shortages, resource depletions, and environmental pollution is bioprocessing. Bioprocessing is a technology that uses microorganisms to produce medicines, biochemical materials, and biofuels—all of which can be derived from microbial biomasses.

Owing to inefficient stain construction, screening, and process development, traditional bioprocessing methods require a lengthy timeframe between development and manufacturing. Comparatively, ABDM incorporates cutting-edge equipment such as miniature bioreactors, high-throughput technologies for screening and process development, quality by design (QbD) methods, and process analysis technology (PAT). The use of ABDM will result in higher predictability during the scale-up and manufacturing stages, as well as higher efficiency, safety, and quality during production at much lower costs.

2. Challenges in advanced bioprocess development and manufacturing

In 2012, the Director of the Office of Biotechnology Products at the US Food and Drug Administration, Steven Kozlowski, M.D, stated the following:

"The challenge in producing bio-products using a cell-based platform is how to develop a robust process with optimal cell-growth conditions within a short timeframe. A product must be delivered which meets market requirements in terms of quality, safety, and cost, and in manner that anticipates potential issues during technology transfer and commercial production."

This statement clearly identifies the challenges faced by bioprocessing. The short development timeframe, robust process, and predictability during technology transfers, scale-up, and manufacturing make this process difficult to achieve. Based on the previous statement, to counter pandemics and satisfy the demands of precision medicine, ABDM must significantly reduce the development and manufacturing timeframe, which is the primary challenge when developing an advanced technology platform.

Pandemics have a sudden, variable, and unpredictable nature that significantly challenges the rapid development and manufacture of a corresponding vaccine. Precision medicine requires that drug products be diversified and produced at reduced scales while remaining affordable. These requirements cannot be satisfied by traditional process development and manufacturing methods, and pose certain challenges for ABDM.

Compared to traditional process development and manufacturing methods, ABDM will result in evolutionary changes. The critical technologies and key equipment used in each process unit must be upgraded accordingly [9]. Table 1 summarizes the key equipment and relevant critical technology platforms used in ABDM.

3. Key equipment and core technologies used in advanced bioprocess development and manufacturing

Miniaturization of key equipment is a prerequisite for the application of high-throughput technologies, which is the most promising strategy for reducing the development timeframe. From the screening to the process development stages,a high-throughput and automation are only possible through miniaturization. During the manufacturing stage, high efficiencies can be achieved using modular operation units and flexible manufacturing systems that produce multiple products in parallel. Such equipment and technologies constitute the core technology platform of ABDM.

3.1. Key equipment and technologies used in bioprocess development

Using traditional process development methods, initial biological candidates enter the bioprocess development stage and undergo primary screening with hundreds of other potential strain candidates. A reduced number of potential strain candidates from the initial pool then advance to a secondary screening. This screening process is commonly conducted using shake flask experiments. However, the use of such experiments as a screening tool has come into question because the results differ greatly from the fermenter/bioreactor results used in process development and manufacturing [10]. Such key differences range from the vessel geometry to the configuration, and may result in

Table 1. Key equipment and critical technology platforms used in ABDM.

	Target attributes	Key equipment	Critical technology platforms
Research and Development	Highly efficient development, reduced development time	Micro- and mini-bioreactor	High-throughput screening, high-throughput process development, process analysis technology, design of experiment (DoE), QbD
	Predictable, scalable, robust, and flexible manufacturing process	Micro- and mini-bioreactor	High-throughput process development, DoE, QbD
Manufacturing	Highly efficient manufacturing process, suitable for multiple products, significantly reduced production time	Disposable product	Disposable technologies, unit operations and modular manufacturing, process platforms, flexible manufacturing, continuous production
	Products meet quality, safety and efficacy requirements		Modular units for process operations, plug-and-play platform, environmental monitoring, raw material quality control

the best strain selected from the shake flask experiment differing from the best strain occurring during large-scale production.

3.1.1. Micro- and mini-bioreactors

Micro- and mini-bioreactors are comparable to conventional bench top bioreactors, with the addition of online monitoring and accurate control loops for parallel controls. Processes and experiments that use parallel bioreactors often scale better to larger bioreactors because of the close simulation of cell growth and product production. The potential of high-throughput platforms is enhanced by the data provided by micro- and mini-bioreactors, resulting in greater predictability, scalability, and robustness, fulfilling the needs of ABDM.

Compared with traditional strain screening and process development methods, micro- and mini-bioreactors offer the following advantages.

- Shorter timeframe at reduced costs: The high-throughput technology platform of micro- and mini-bioreactors results in reduced development times and costs.
- Reliable experiment results: Owing to their high comparability, the screening results from micro- and mini-bioreactors more accurately reflect the actual manufacturing conditions.
- A larger amount of data obtained: Even during the strain screening, early process development, and optimization stages, using miniaturized bioreactors allows a deep understanding of the bioprocess and strain properties to be achieved, which provides the foundation for a high-quality database for a future process scale-up and manufacturing conditions.
- Improved predictability: The application of high-throughput technology, DoE, and PAT in miniaturized bioreactors can improve the predictability of the cell performance at the manufacturing scale.

3.1.2. High-throughput technologies supported by a large database and robotic automation

High-throughput technology (HTT) can provide fast, automatic, and parallel sampling for data gathering. Compared to traditional data collection techniques, HTT can increase the development efficiency by orders of magnitude. The HTT used during the bio-process development is called high-throughput process development (HTPD), and can provide a deep understanding of both processes and products. Related tools and technologies include automation, miniaturization, parallelization, continuous manufacturing, effective DoE, complicated data acquisition and analysis, building blocks, and virtual screening [11].

In recent years, miniaturized platforms offering high throughput, scalability, and disposable techniques have been widely used in rapid process development and optimization. These platforms possess the following three key characteristics:

(1) miniaturization enabling a faster experiment throughput at a lower cost,
(2) automation supporting an accurate, reproducible performance across a large number of individual operations, and
(3) parallel processing supporting the evaluation of a wide experiment area and enhancing our understanding of the process.

Miniaturized bioreactors and high-throughput technologies represent the fundamental hardware platform and software technology in ABDM. Building upon the high-throughput screening and development capabilities afforded through miniaturization, the next steps for ABDM are the execution of the unit operations in a modular manufacturing platform.

3.2. Key technologies used in manufacturing

3.2.1. Disposable technologies

In the biopharmaceutical industry, *disposable* refers to single-use consumables, products, and equipment. These combined consumables, products, and equipment form a *disposable system*; technologies based on this system are referred to as *disposable technologies*.

Compared with conventional stainless-steel equipment, disposable bioreactors offer the following advantages: reduced product launch times, improved production efficiencies, reduced production costs, improved product quality, simplified process control, improved manufacturing robustness, reduced unit operations (by eliminating the cleaning and sterilization steps), and reduced equipment validation times and costs in the current good manufacturing practices (cGMP) environment [12].

Disposable technologies can increase manufacturing suite utilization and decrease energy consumption. Disposable technologies also offer advantages related to capital expense, raw material costs, safety, rapid deployment, fast turnaround, and process reproducibility. As shown in Fig. 1, a flexible manufacturing process based on disposable technologies can save 60% in capital expenses, 40% in the amount of space required, 80% in the amount of water and disposable waste, 32% in overall costs, and 60%–75% in construction time compared with traditional manufacturing methods [13].

3.2.2. Plug-and-play modular platforms

Plug-and-play modular platforms and disposable technologies are closely related. In flexible manufacturing, the construction of the manufacturing suite, modular design, and production pipeline are all based on disposable technologies. With the platform technology, each individual modular suite in flexible manufacturing can be used to process different host cells, including mammalian cell cultures, E. coli, yeast, fungi, and insect cells. When multiple bioprocess unit operations, such as fermentation and purification, are connected, a complete bioprocess manufacturing operation is formed.

4. High-throughput miniaturized bioreactors

Within the larger spectrum of fermentation technology used in the process sciences, two primary types of high-throughput bioreactors are used: micro-bioreactors with a total working volume of 0.1 to 15 mL, and mini-bioreactors with a total working volume of 15 to 500 mL. Micro-bioreactors have a higher throughput and are primarily used for cell line screening work, including mammalian and insect cell lines that have a relatively slow growth rate. Mini-bioreactors have a larger working volume and are more comparable to lab-scale bioreactors with respect to their control systems, working environment, and vessel construction and configuration. At present, most mini-bioreactors can perform high-density cell cultures (fermentation) for both mammalian cell lines and microbes.

4.1. Off-the-shelf micro-bioreactors

Based on their operational principal, commercially available micro-bioreactors can be classified into three categories: bubble/air permeable systems, stirred systems, and shaken systems, each of which is described more fully below.

4.1.1. Bubble/air permeable micro-bioreactors

Fig. 2 shows a representative bubble/air permeable micro-bioreactor used in the SimCell automation management system. This figure provides both an overview of the system and a magnified view of the micro-bioreactor design.

Intended for use in high-throughput cell culture process development, SimCell systems contain an array of six independent micro-bioreactors with a working volume of up to 700 µL. Using robotic management and a highly automated control system, SimCell systems are able to perform up to 1260 simultaneous cell culture experiments. Despite these capabilities, SimCell systems are not commonly used in the biotechnology industry because of the high system and maintenance costs, and the complex operations required [14].

4.1.2. Stirred micro-bioreactors

Fig. 3 shows a representative stirred micro-bioreactor, i.e., an AMBR15 from Sartorius.

The AMBR15 system is an advanced micro-bioreactor commonly used in the biotechnology industry. This automated system can run and evaluate 24 or 48 stirred micro-bioreactors in parallel on a working platform. With a working volume of 10 to 15 mL, each micro-bioreactor has an independent control system that controls such process parameters as the temperature, dissolved oxygen (DO), and pH. Currently, the AMBR15 system is mainly used in early-stage cell culture process development.

4.1.3. Shaken micro-bioreactors

Fig. 4 shows representative shaken micro-bioreactors. The

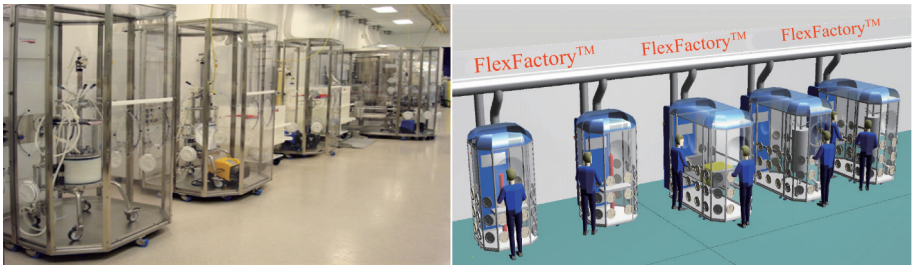

Fig. 1. Modular production units and FlexFactory™

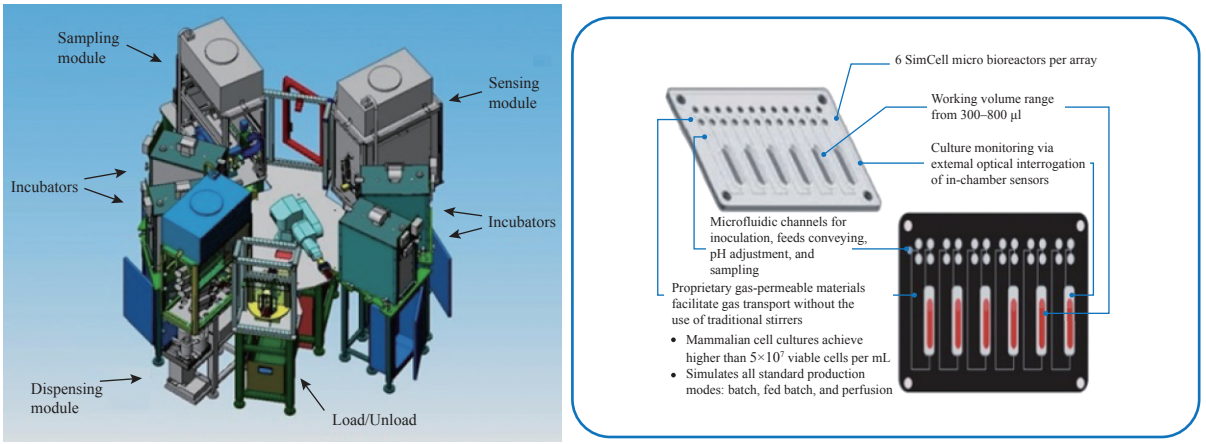

Fig. 2. SimCell automation management system and its bioreactor design.

systems shown are the Micro-24 system from Pall (left) and the next-generation micro-Matrix system from Applikon (right).

The Micro-24 system is able to run 24 parallel experiments during which each micro-bioreactor independently controls its own gas supply, temperature, and pH. The working volume for each micro-bioreactor is less than 10 mL. This system has proven to be a useful tool for both mammalian cell cultures and microbial fermentation, and its scalability has been well documented [15].

In 2014, Applikon launched a next-generation micro-bioreactor system, the micro-Matrix. With its precision feeding system, the micro-Matrix system enables high-density cell cultures for both microbial fermentation and mammalian cells.

4.2. Off-the-shelf mini-bioreactors

Compared to micro-bioreactors, mini-bioreactors offer a number of advantages.

- Better independent monitoring and control systems that can generate more process information.
- High automation and the capability to run experiments in parallel.
- Comparable to lab-scale bioreactors.
- Able to accurately mimic the growth kinetics and product expression during the manufacturing process.
- Feasibly scalable based on process parameters such as the stirring speed, constant DO, oxygen mass transfer, and mixing time.
- Able to offer a growth environment similar to that of a lab-scale bioreactor (limited to stirred mini-bioreactors).

Mini-bioreactorsare currently used for DoE studies. The most widely used commercially available mini-bioreactors are the AMBR-250 system from Sartorius and the DASbox system from Eppendorf.

The AMBR 250 system includes 12 or 24 independent mini-bioreactors and has a working volume of 100 to 250 mL. Two different system designs can satisfy the different needs for mammalian cell cultures and microbial fermentation. Comparatively, the DAS box parallel system functions using working modules. Each module consists of four sets of mini-bioreactors; 24 or more sets of mini-bioreactors can be connected and run in parallel. The DAS box system, depicted in Fig. 5, can be used for both mammalian cell cultures and microbial fermentation. Both theAMBR-250 and DASbox systems have high repeatability and scalability and are suitable for process development and DoE studies [16].

Fig. 3. AMBR15 micro-bioreactor.

4.3. Current and future prospects for miniaturized bioreactors in China

Bioreactors are currently one of the weakest technologies in China's bioprocess development and manufacturing industry;their development lags far behind similar technologies in western countries. China does not currently offer any domestic miniature bioreactor products. Instead, all miniature bioreactor technologies are purchased from other countries at a high cost and without the intellectual property rights.

5. Potential for advanced bioprocess development and manufacturing

In recent years, countries such as China have begun emphasizing structural adjustments and development models in strategic emerging industries. These countries may achieve

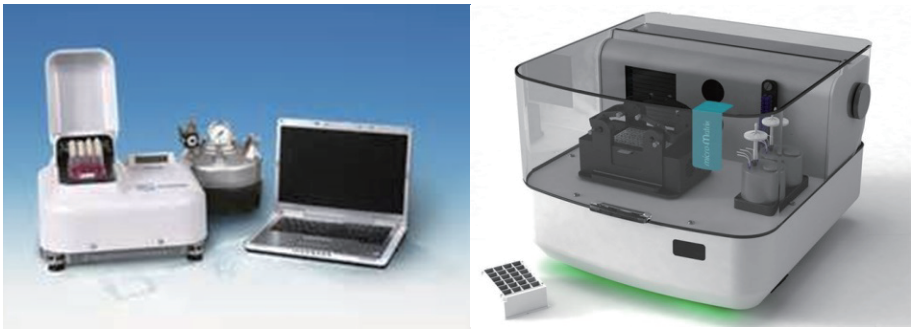

Fig. 4. Micro-24 micro-bioreactor (left) and micro-Matrix (right).

Fig. 5. DASbox mini-bioreactor.

breakthroughs in these emerging industries, which will boost their overall competitiveness in science and technology. The Chinese and American governments face similar situations and challenges underthe threat from various disasters. Advances in ABDM will enable arapid response to unpredictable events such as influenza pandemics or bioterrorism and subsequently improvetheirnational security and defense capabilities. China can learn fromtheUS efforts regarding national organizational structures, research and development investments, and legal and policy issues.

Advances in ABDM will directly affectthedevelopment in several different industries (e.g., biopharmaceuticals, vaccines, precision medicine, and biomanufacturing) and result in significant economic benefit. For example, the current global biopharmaceutical market is estimated at 400 billion US dollars and is expected to reach 500 billon US dollars within the next five years.Vaccines, which are important for national security, had a market value of 24 billion US dollars in 2014, and are estimated to exceed 100 billion US dollars by 2025. The emerging field of precision medicine had a market value of 60 billion US dollars in 2015, which is expected to increase at an annual rate of 15%. Other fields that will be impacted by advancements in ABDM include biofuels and wastewater treatment.

Advanced bioprocess development and manufacturing will fundamentally change the traditional technology platform and introduce new concepts in the fields of biopharmaceuticals, medical treatment, and disease prevention and control. The emergence of precision medicine has revolutionized the traditional medical industry. With the development of detection methods for precision medicine, additional targets for its use have been found;however, the development of methods to quickly and economically produce medications with the level of diversity required by the field of precision medicine has received significantly less attention. Precision medicine can only be realized by applying ABDM, along with early stage gene detection and diagnosis methodologies.

In summary, after first learning from other nations regarding the methods required for innovation, China will then be able to establish its own ABDM and national rapid response systems. The combined results will improve our national security, economy, and public health.

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