cell culture equipment.

TRENDS AND ENGINEERING CHALLENGES IN CELL CULTURE MANUFACTURING

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About NXTGEN Hightech: The project has been made possible through funding from the National Growth Fund program NXTGEN Hightech, which runs until 2030. With over 330 partners, more than 60 projects, and six key domains, NXTGEN Hightech is backed by an investment of €1 billion. This initiative plays a pivotal role in fostering sustainable economic growth in the Netherlands, while addressing critical societal challenges in energy transition, healthcare, safety, and food. For more information, visit www.nxtgenhightech.nl.

1. INTRODUCTION

In recent decades, the biotech market has experienced significant growth, driven by innovations such as single-use technologies, advanced cell lines, and state-of-the-art bioreactors. The need to reduce costs, improve speed and efficiency, and scale production effectively has been a major catalyst for progress in bioprocessing.

Cell cultures play a pivotal role in addressing future healthcare challenges. For instance, cell therapies—where cells are used as treatments—demand the cultivation of high-quality cells. Similarly, controlled and reproducible cell cultivation is essential for other applications, including Lab-on-Chip systems, Organ-on-Chip platforms, and vaccine and viral vector production. Automating cell culture processes can not only standardize product quality but also significantly reduce personnel costs and increase yield. Achieving this requires the integration of advanced technologies, such as cutting-edge sensors, to monitor and control production processes with precision.

The Dutch Growth Fund Consortium NXTGEN Hightech Biomed05 aims to develop next-generation cell culture equipment by leveraging innovative sensor technologies, automation, and microfluidic integration. This initiative seeks to enable more precise control over cell culture processes, resulting in superior-quality cell and cell-derived products. The consortium brings together diverse stakeholders from across the value chain—including CDMOs, cell therapy developers, and technology and materials providers—who collaborate to identify unmet needs and anticipate industry and regulatory requirements.

To deepen insights into the technological demands of cell culture applications, consortium partner Demcon organized a workshop involving external experts and other NXTGEN Hightech partners. The workshop's objective was to establish a comprehensive understanding of the most critical technologies and competences required for cell culture manufacturing and to explore potential areas for collaboration within the consortium.

The primary focus areas for cell culture applications in the workshop were:
- Manufacturing technologies for cell and gene therapy
- Tissue engineering
- Biopharmaceutical manufacturing

This document provides in Chapter 2 a summary of the workshop, highlighting emerging trends in cell culture manufacturing processes and identifying current and future technological challenges in the field. In Chapter 3 concluding remarks and the relation to NXTGEN Hightech activities will be described.

2. CELL CULTURE MANUFACTURING

2.1 Generic trends and challenges in bioprocessing

During the workshop some general trends and challenges were identified:

Automation and closed-loop systems
The bioprocessing world is moving away from manual work and toward *automated systems* at all stages, like seeding, expansion, differentiation, purification, and fill/finish. The main goal is to cut down on hands-on work, reduce reliance on operators, boost efficiency, minimize errors, and lower production costs. Many companies stick to proprietary platforms for automation and *closed-loop bioprocessing* to protect their know-how, maintain strict control over key processes, and stay ahead of the competition. These systems are tightly controlled to ensure consistency in critical operations.

Locked-in versus open platforms
Locked-in platforms come with pre-validated, all-in-one solutions that save time, simplify workflows, and offer great customer support while making it easier to scale up production. However, the biotech industry is also shifting toward more *open platforms*. Open systems bring flexibility, *standardization*, affordability, *scalability*, and regulatory benefits. Even so, locked-in systems are still widely used in certain areas where reliability and seamless integration are absolutely essential.

Artificial intelligence
Artificial intelligence (AI) is becoming increasingly important in healthcare and biopharma by changing how we analyze data, make decisions, and automate processes, especially in drug development and bioprocessing. AI is being used to optimize processes, scale up production, automate tasks, and create "*digital twins*" for simulations and quality control that save money. These tools speed up production, ensure consistent product quality, and deal with the unpredictable nature of biological systems. Since the pharmaceutical industry prioritizes patient safety and regulatory compliance, AI applications go through strict validation. But there are still challenges, like data biases and the mysterious "black box" nature of some AI models. To use AI effectively and ethically, the industry needs more expertise to address these issues. Still, AI is becoming a must-have for making bioprocessing faster, more scalable, and more reliable.

Real time monitoring

Cell culture processes are becoming increasingly complex, particularly with the advent of continuous bioprocessing. As a result, the industry is increasingly adopting advanced technologies such as *in-line sensing* and *automated sampling*. These tools help keep processes running smoothly, ensure consistent product quality, and reduce the need for hands-on work. *Real-time monitoring*, automated sampling, and *data-driven decisions* are game-changers. As the industry moves toward *continuous biomanufacturing*, these technologies are critical for maintaining quality, improving efficiency, and scaling up production.

Cryopreservation

Cryopreservation and transport are big challenges for cell and gene therapies. Keeping cells intact during shipping and meeting strict *regulatory requirements* isn't easy. Advances in cold chain technology are making things better by improving efficiency, scalability, and reliability throughout the supply chain. But there's still work to do. The growing need for personalized medicine means we'll need even more innovation and better alignment with regulatory standards to keep up.

Technology key words:

automated processes, closed-loop bioprocessing, open platforms, continuous bioprocessing, artificial intelligence, digital twins, scalability, regulatory compliance, in-line sensing, automatic sampling, real-time monitoring, data-driven decision making, cryopreservation

2.2 Emerging trends and challenges in Cell and Gene Therapies (CGT)

The field of cell and gene therapies comes with some additional unique manufacturing challenges.

Scalability and cost-efficiency

For both autologous and allogeneic cell therapies, as well as in vivo and ex vivo gene therapies, the focus is on keeping production as cost-efficient as possible. While "off-the-shelf" allogeneic therapies show promise, market approvals remain limited because of issues like *immune reactions*, *iPSC variability*, and the slow pace of automation adoption. On the other hand, autologous CAR T-cell therapies are gaining a lot of attention and investment, which makes streamlining and automating these processes a top priority. Efforts in bioprocessing are all about scaling up production and cutting costs to make these expensive therapies more accessible—especially for treatments like CAR-T. These therapies cost anywhere from $373,000 to $1 million per treatment due to their highly personalized production process and intensive *quality control* [1]. Moreover, cell and gene therapies (CGTs) face significant reimbursement challenges. Since reimbursement models often fail to fully cover the associated costs, hospitals are left to bear substantial financial burdens when providing treatments such as CAR-T [2].

Autologous therapies are custom-made using material from individual patients, which means they need high-quality, viable T cells that are grown in controlled environments. Bioreactors with dynamic perfusion cultures play a key role here, but T cells are notoriously sensitive, adding a layer of complexity. Deciding between centralized and decentralized biomanufacturing ultimately depends on factors like the type of therapy, cost, speed, flexibility, and logistical considerations.

Decentralized and point-of-care solutions:

Gene therapies, still a relatively new field since their rise in the early 2000s, face challenges in scaling production, reducing variability, and making treatments affordable for larger patient groups. One promising development is *Point-of-Care* (POC) gene therapies, which have the potential to revolutionize the delivery of advanced treatments. Instead of manufacturing these therapies in remote facilities, they could be produced and administered directly at the point of care, such as in hospitals or clinics. This localized approach offers clear advantages, including the ability to personalize treatments and accelerate delivery by reducing vein-to-vein time. However, to turn this vision into reality, the industry must develop modular, integrated, and automated bioprocessing systems.

Such decentralized production isn't without challenges, especially when it comes to meeting regulatory standards. Adjusting *GMP* (Good Manufacturing Practice) standards for decentralized setups is tricky. There's a need for robust *quality control* (QC) and *monitoring technologies* to ensure consistency, and everything must be standardized to maintain the same quality across multiple sites. Without clear protocols and streamlined processes, maintaining uniformity will be a tough hurdle to overcome.

Additional technology key words:
immune reactions, IPSC variability, perfusion, point-of-care systems, quality control, monitoring technologies, standardization, GMP

2.3 Emerging trends and challenges in Tissue Engineering

Tissue engineering brings together scaffolds, cells, and biologically active molecules to create functional tissues that can repair, improve, or even replace damaged organs. The goal is to design constructs that replicate or enhance the natural functions of tissue. Since this field uses cells, many of the challenges mentioned earlier also apply to tissue engineering.

Macro-tissue assembly
Successful breakthroughs in micro-tissues, like organoids and "human body on a chip" systems, are pushing drug testing and personalized medicine forward. To apply these innovations to "macro-tissues" for real-world tissue engineering, there's still a need for more research, funding, and efforts to translate findings into clinical practice. Beyond cell culturing issues, tissue engineering faces additional hurdles like *vascularization*, finding reliable cell sources, and advancing *scaffolding* techniques such as *3D bioprinting*. Future innovations in areas like *mechanical stimulation*, *bio-instructive materials*, and even *xeno-transplantation* could play a big role in taking this field to the next level.

Despite existing challenges for bringing new tissue engineered products to the market, several tissue regenerative products using cells are already commercially approved for clinical use. These products are mainly in the field of skin, bone, cartilage and corneal regeneration. Some examples across different applications are:

- **MACI (Matrix-Induced Autologous Chondrocyte Implantation, Vericel):** Uses autologous chondrocytes expanded in vitro and embedded on a collagen scaffold to repair knee cartilage defects.
- **Osteocel (NuVasive):** A cellular bone allograft containing viable mesenchymal stem cells (MSCs) for bone repair.
- **Epicel (Vericel):** Autologous cultured epidermal cells for patients with severe burns covering large areas.

Ethical and regulatory constraints
Just like in cell and gene therapies, tissue engineering also struggles with regulatory challenges. Aligning GMP practices, tackling *ethical concerns*, ensuring quality control (QC), and achieving standardization are all ongoing issues. To overcome these barriers and make these groundbreaking treatments safely available to patients, collaboration between regulators, industry leaders, and academic researchers will be essential.

Additional technology key words:
Vascularization, scaffolding, 3D bioprinting, mechanical stimulation, bio-instructive materials, xeno-transplantation, ethical considerations

2.4 Emerging trends in Biopharmaceuticals

Biopharmaceuticals, such as monoclonal antibodies (mAbs), vaccines, and recombinant peptides, rely on highly sensitive production cells, making stable production processes critical for ensuring product quality. The mAbs demand remains a core growth driver due to their significant role in top-selling drugs, particularly for personalized therapies offering tailored and effective treatments. While smaller biotech firms face funding challenges that can slow progress, long-term prospects are strong, supported by continued investments in advanced therapies.

To keep up with demand, the industry is focusing on high-performance cell lines, cutting-edge culture systems for high cell density, and automated, closed production processes. These advances are set to boost efficiency, scalability, and product quality in biopharmaceutical manufacturing. However, high production costs remain a major challenge. Producing mAbs involves big investments in bioreactors, culture media, and purification systems, driving up expenses. That's why buzzwords like automation, scalability, continuous processing, in-line quality control, AI, and advanced data analytics are becoming increasingly important.

The past decade has seen a narrowing of the gap between cell biology and process engineering. This shift is largely due to the growing demands of mAb manufacturing and advances in automation and data analytics. Looking ahead, the future of biomanufacturing will depend on blending biological insights with engineering expertise to tackle the complexities of personalized medicine and advanced biologics.

Another area gaining attention is the use of *organ-on-chip* models. These offer better, more predictive results during preclinical testing, which can save time and resources in drug development.

Last but not least, also on the sustainability front, there is growing interest in *designing for recycling*. The industry currently generates significant waste, with high volumes of single-use plastics like bioreactor bags and filters. Addressing this issue will be key to creating a more sustainable future for biopharmaceuticals.

Additional technology key words:
Interdisciplinary collaboration, organ-on-chip platforms, design for recycling

3. CONCLUDING REMARKS

All the technology keywords discussed during the workshop have been compiled in Figure 1 (size does not indicate weight or priority). A central theme emerging from the workshop was the pressing need for greater automation in closed-loop cell culture systems. Key technological advancements critical for optimizing processes, achieving scalability, and reducing manufacturing costs include real-time monitoring through in-line sensors and the application of *artificial intelligence* for process control. These innovations aim to make bioprocessing faster, more scalable, and more reliable.

The workshop's outcomes, combined with a questionnaire to identify unmet needs across consortium partners, will guide the development of next-generation cell culture equipment under the NXTGEN Hightech Biomed05 program. Through the creation of demonstrators, new sensing technologies and solutions for integrating process equipment into closed-loop systems will be developed. The first demonstrator, an automated sampling system, is already under development. Based on the workshop findings and questionnaire responses, additional demonstrators will be defined and realized to solve commonly shared challenges in cell culture processes. Successful demonstrators will then in a later stage be further refined for implementation in a fully GMP-compliant environment.

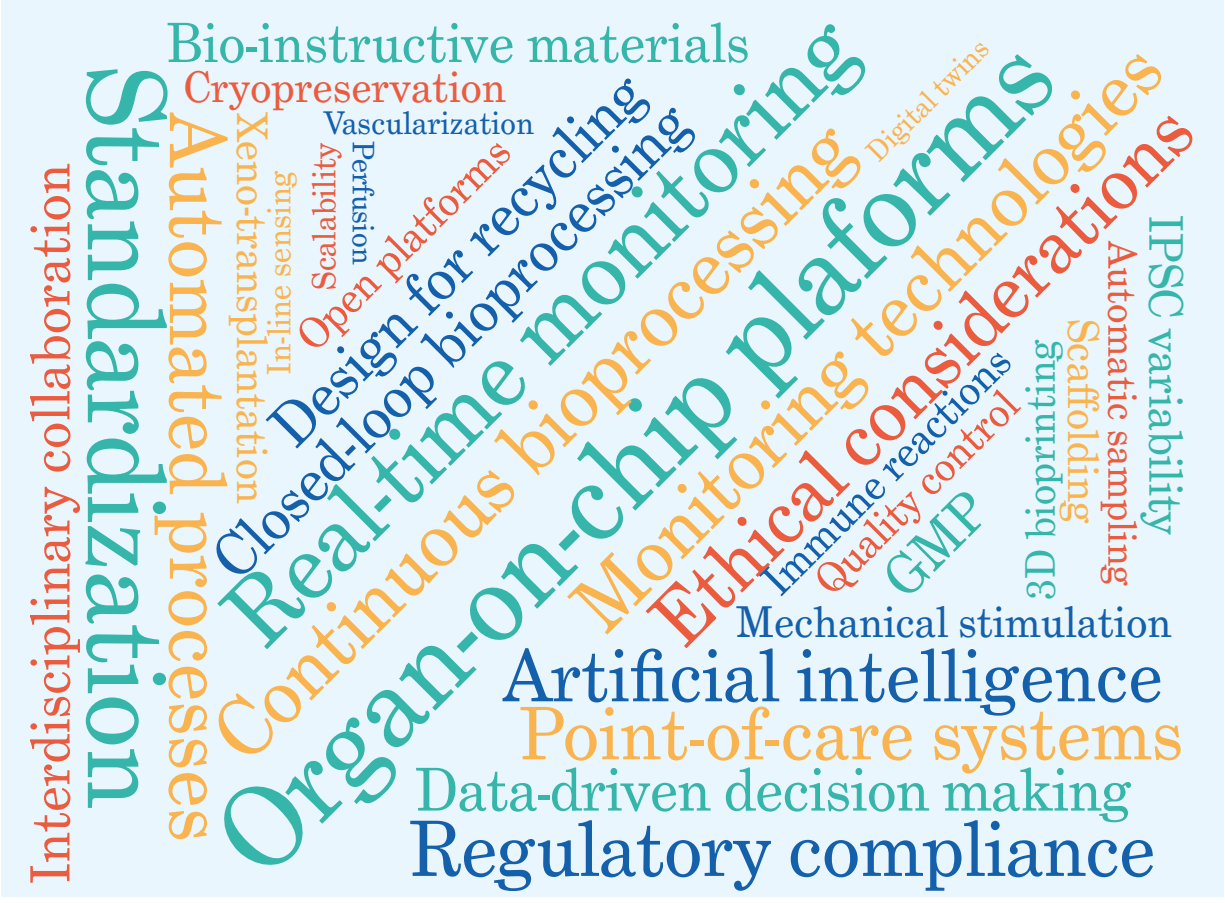

FIGURE 1

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