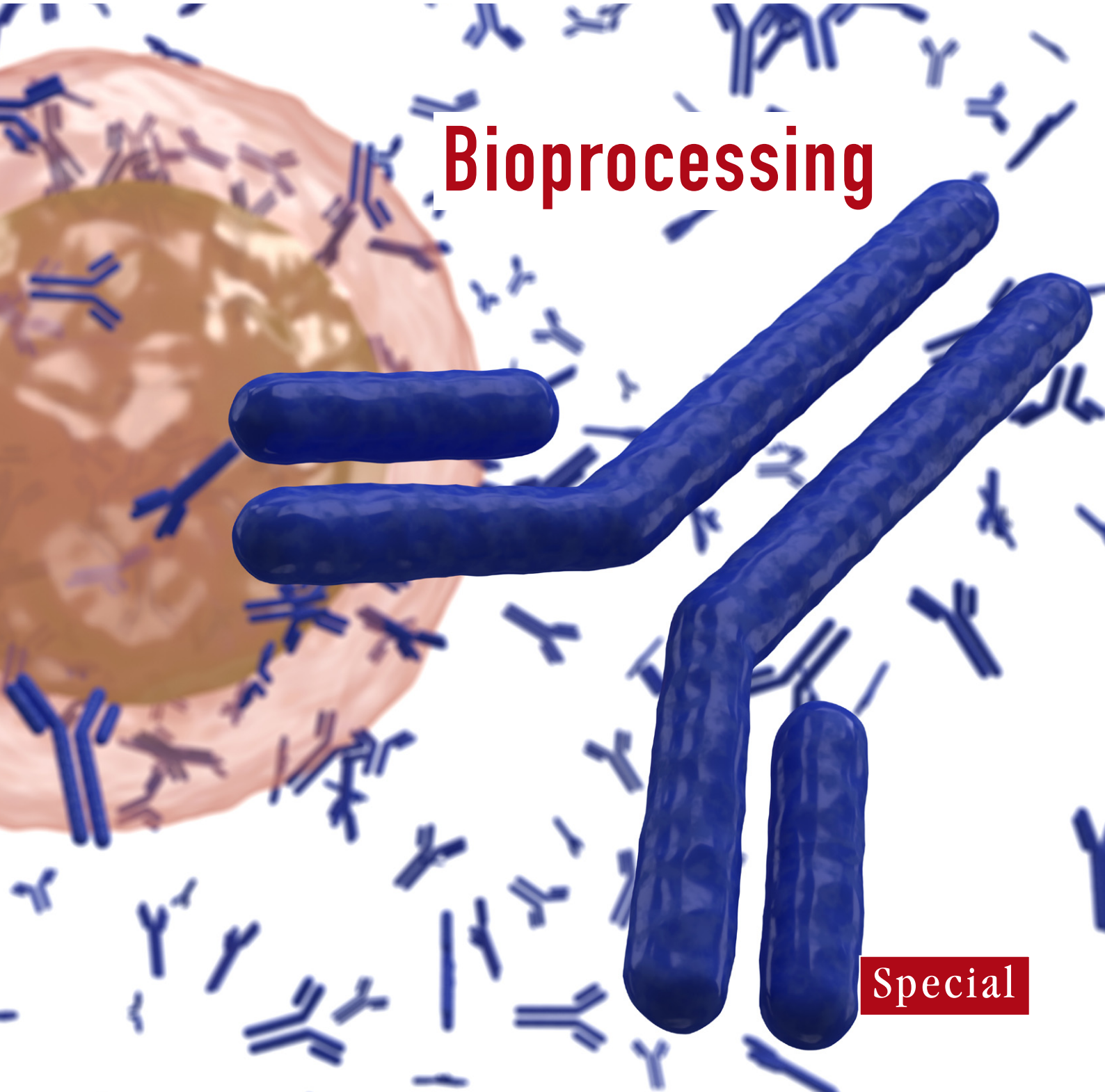
European Biotechnology

Spring 2019

Bioprocessing



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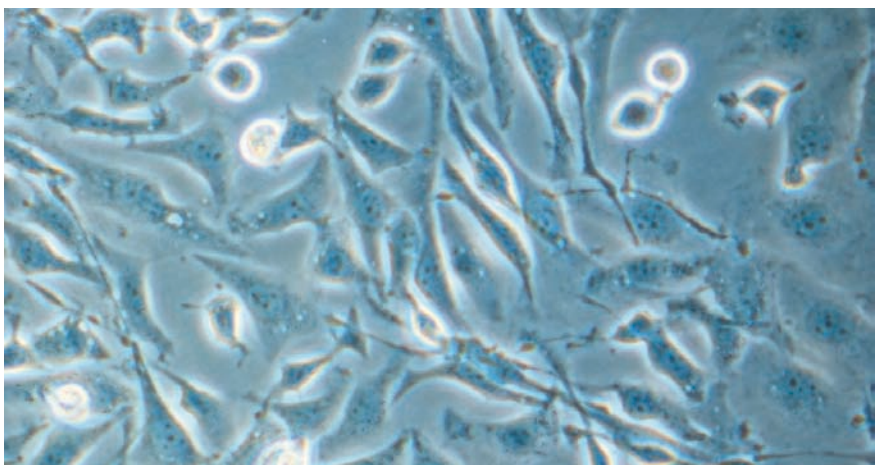
Bioengineers to standardise biomanufacturing

BIOMANUFACTURING Biomanufacturing – either for production of biologics or bio-based everyday products – has traditionally suffered from the unpredictably variable response of production cell lines to external stimuli. Synthetic biology groups now wish to create a network of biofoundries that aim to establish reproducibility standards from process design to product purification and – in the long term – intend to switch from cell-based to cell-free bioproduction.

As Big Pharma's development pipeline shows growing amounts of next-generation engineered antibody formats, further complexity has been added to the process development and biomanufacturing of biologics. "Today, we have more than 100 different formats for biospecific antibodies alone", says Thomas Schirrmann, CEO of antibody discovery and development specialist Yumab GmbH (Braunschweig, Germany). Yumab cofounder Stefan Dübel confirms that "classical mAbs today make up only a third of all drug candidates in the development pipeline of companies like Roche." The newly-engineered antibody formats, together with the current hype around cell and gene therapies, are new challenges for Contract Development and Manufacturing Organisations (CDMOs) that currently expand their scientific and technological capabilities to satisfy the new demand.



Adherend Chinese hamster ovary (CHO) cells in cell culture flask (phase contrast microscopic view)

Challenges in production

As the complexity of drug formats is growing, companies have begun to look for alternative production systems including CHO cells, the workhorses of mAb manufacturing: MedImmune has partly switched to HEK293 cells that provide human glycosylation of therapeutic proteins. Biogen and MIT have begun to systematically screen for alternatives to CHO cells, which they say is not the system to master future challenges in USP, DSP, and QBD. Florian Wurm, one of the biomanufacturing pioneers at Genentech during 1990s, knows the reason. The lack of reproducibility of CHO-cell-based biomanufacturing is due to the non-existent clonality of cell lines. "Even the original immortalised hamster cell lines of 1957 were just aneuploid, quasi-diploid cell populations that are highly genetically variable," he stressed at Rentschler Biopharma's 5th Biotech Days. It's no wonder that the heterogeneous CHO cell populations stochastically adapt if any selection pressure occurs during a process, i.e. different culture conditions, process scale up, etc. Even miniaturised, automated bioprocess development, or quality by design, have only gradually improved the imminent problems of standardisation of the challenging CHO cell system.

Cell-free processes

Yet, it sounds like science fiction. But bioengineers at German Fraunhofer Gesellschaft have already begun to establish cell-free systems for bioproduction, as they provide critical advantages to call-based systems, such as a:

- fast synthesis rate
- direct reaction control
- tolerance to toxic products
- scalability.

Pictures: Alcibiades

Another approach, most recently tested by MSD, is establishing programming languages that can detect the interactions between different experimental factors. In order to create a microbial manufacturing platform for biologics, MSD used the language ANTHA, which examined the interaction between 27 factors from 576 experiments to integrate strain construction with process development – a task that is far too complex to address with a screening approach.

Synbio crucial for bio-based conversions

Another emerging application field in biomanufacturing is bio-based production in order to establish a circular bioeconomy. Participants in an illustrious OECD/Imperial College workshop on engineering/synthetic biology in London last September said that they could solve the current quality, reproducibility issues of bio-based processes by applying quantitative engineering rigour to biotechnology through alignment of its methods with the engineering design circle. The key problem, however, is the dearth of interoperability standards in engineering production cell-lines or cell-free systems by means of synthetic biology or metabolic engineering. Working without standards would result in a significant lack of reproducibility and reliability. "As most start-ups lack the resources for fundamental research and as most larger companies are not sufficiently incentivised in the face of policy uncertainty to establish synbio standards, public-private partnerships would be a solution," said James Philp from OECD in Paris. Such biofoundries would develop and integrate standardised, industrially relevant production strains, advanced tools for bioengineering and data analysis, and process development. Biofoundaries might be viewed as small-scale production plants for iterative opimisation of bioprocesses that could be later applied in industrial biorefineries or production plants for biopharmaceuticals. By providing such a standardised toolbox, biofoundries contribute to a distributed, decentralised manufacturing model "Public-private biofoundries would prevent high-risk investments for companies and de-risk novel engineering biology technologies," said Philp. "There are currently few biofoundries, but Europe is in an advantageous position." Furthermore, the OECD is currently working to establish a global network of biological resource centres that will enhance access to biological resources. Philp told European Biotechnology that he thinks it will take at least five years to establish some standardisation in engineering biology. He says biofoundries would also provide solutions for bio-based products manufacturers. ■

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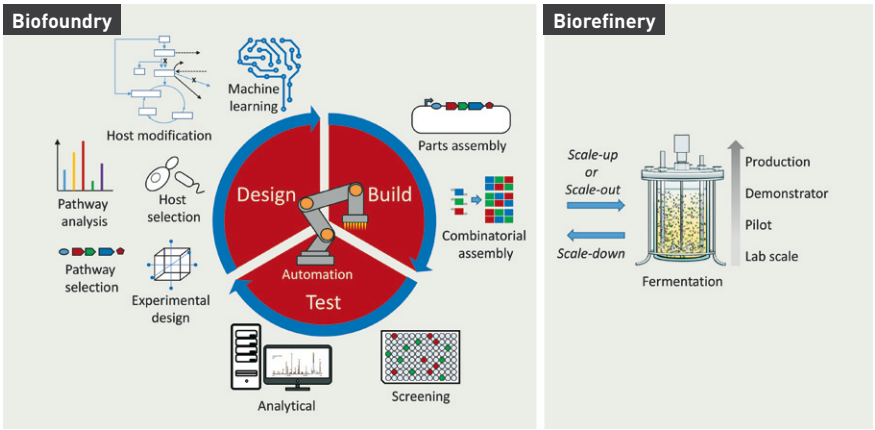

Worksharing between biofoundries and biorefineries within a modern, synbio-enabled bio-economy

Pictures: James Philp, OECD

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Automation integration in biomanufacturing

BEST PRACTICE AUTOMATION INTEGRATION Successfully integrating automation in a biomanufacturing environment can become a daunting task without the right preparation and a clear implementation strategy. Through proper planning, one can eliminate costly errors and missteps and focus on developing efficient, future-proof automation strategies.

› By Scott Mangiacotti, GE Healthcare Life Sciences, and Trevor Marshall, Zenith Technologies

For some time, the pharmaceutical industry has been confronted with a dramatic evolution of its traditional business model. As broad-spectrum, blockbuster drugs, which offered a substantial payoff, have lost ground, drug developers have turned to the development of targeted medicines for selected patient subpopulations to support personalised medicine and combination therapies. Not only does this evolution call for new approaches to drug pipeline development, but it also increases the need for operational efficiency. Now, greater speed, productivity, and accuracy have gone from being just advantages in a complex manufacturing environment to requirements, leading to more investments in technology and automation. Here Scott Mangiacotti, Engineering Leader at GE Healthcare Life Sciences and Trevor Marshall, Director of global engineering at Zenith Technologies and GE Healthcare Life Sciences go into detail about best practice for integrating automation into biomanufacturing environments.

Automation systems have the ability to provide one with streamlined, centralised control and improved transparency in your manufacturing processes. They can also collect and analyse data that could potentially help accelerate the regulatory review process. This is possible only if your system is appropriately designed, and considerations for its functionality and stakeholder deliverables begin as early in the project as possible. This should start in the initial phases of project development, as part of the concept study phase, where it is important that automation needs and expectations are documented, as well as defined.

Picture: GE Healthcare

Creating a basic facility design

The main purpose of a concept study typically relates to the process requirements and equipment needed to bring a new drug to market at a facility or to perform a transfer of production from one facility to another. The information in the concept study can be at a high level or as detailed as necessary, depending on the type of facility being developed.

The automation strategy serves as a key document, as project execution evolves from concept design, to basic design, and then, to detailed design and execution. Including the automation strategy for the project in the concept study will anchor a project to decisions that underpin the level and complexity of automation and manufacturing systems agreed upon for a project. It also keeps everyone on track by providing the rationale for the key pillars of the project. When different stakeholders or new hires enter throughout the life cycle of the project, the potential for new strategies or ideas regarding the automation strategy can surface. This causes diversions from the original basis for the project, potentially leading to confusion and frustration.

For an existing facility where new equipment is being added, such as new bioreactors, the document can simply state to follow the same approach used in previous projects, if no additional enhancements or integration is necessary or required. This statement creates a clear

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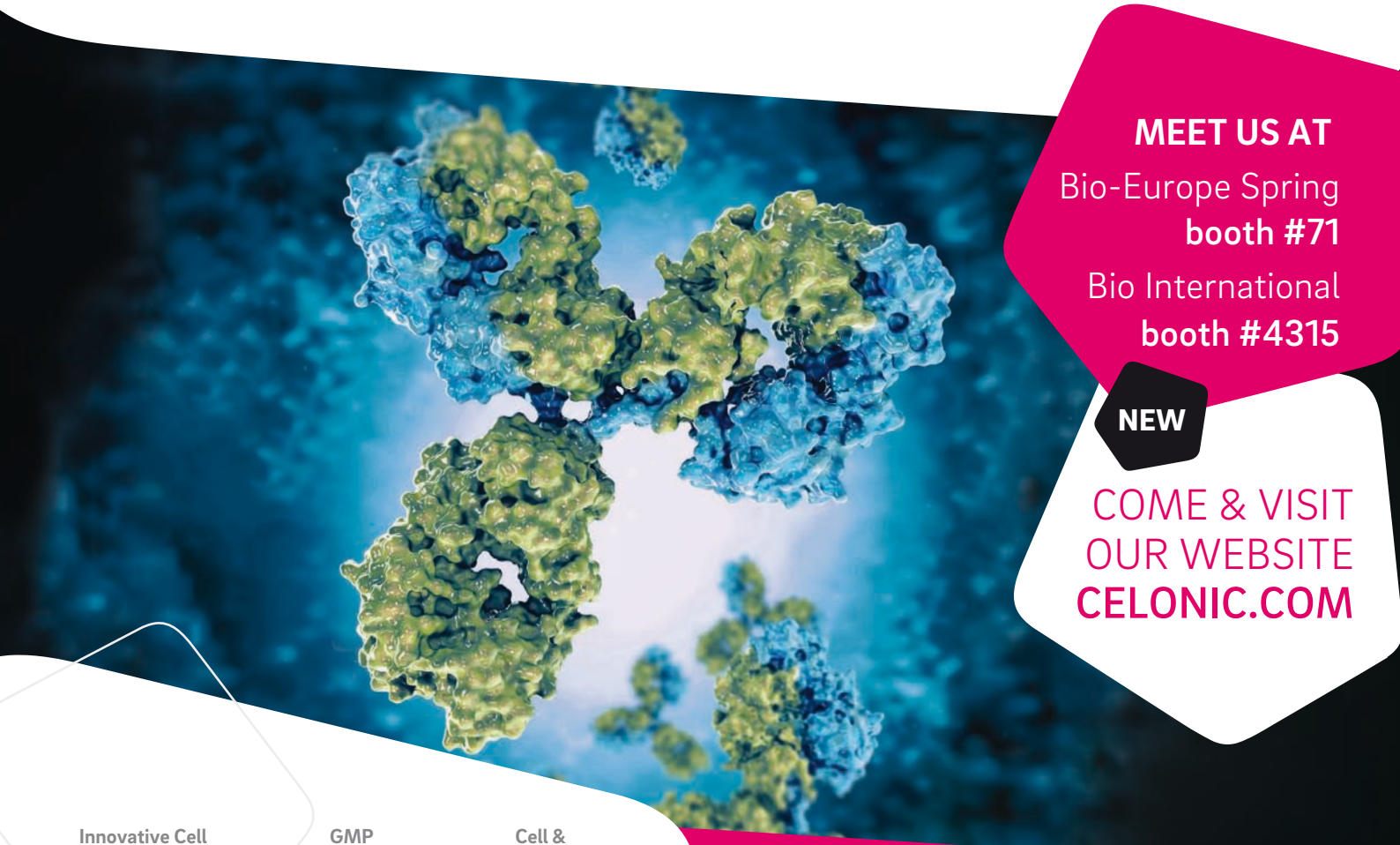

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path forward for the project. For new greenfield facilities, with new manufacturing systems being deployed, it is important to spend an appropriate amount of time during the concept and basic design phase defining the complete scope of the automation project. This includes the level of integration of manufacturing systems across the shop floor, up to the enterprise resource planning systems (ERP). It's quite important to verify that all automation software deliverables are clearly defined so that, as the project progresses, it can be measured accurately and reported on throughout detailed design and project execution. This involves identifying the software elements required and putting the life cycle of each one in the plan, i.e., design, code, and test. The more granular and detailed the plan, the greater the level of accuracy during project execution.

Align expectations

It is critical that the project stakeholders are aligned on the automation scope and delivery from the beginning, to avoid late changes to key design principles, which can add costs and create delays. Both your team and the suppliers must also be aware of the end goal, including schedule and technical and commercial agreements. Identifying what is most important and making compromises, where necessary, creates a plan that satisfies all stakeholders. This means understanding your needs from a technical, schedule, budgetary, and compliance perspective. Do not overdo or underdo any of those expectations, as it will inevitably lead to dissatisfaction. When providing new equipment to an existing facility, take time to understand how it will work with existing equipment, as well as the interface techniques, so the integration is seamless.

Understanding of validation or testing procedures

To ensure a system is going to function as intended once it is up and running and will meet the validation requirements, use good automation manufacturing practices (GAMP) to align validation and testing expectations. Using GAMP also establishes a mutual understanding between you and your suppliers, in terms of the computer system validation process and what is expected from each side for it to be successful. When purchasing specialized equipment or software from a vendor, it is important to include their expertise relative to to the level of testing required at each stage of the project, be it at the vendor's location or on site. Creating trusted relationships with key suppliers builds trust in the supplier's validation and testing processes, while also enabling the supplier to become familiar with a particular customer's expectations or nuances with regards to corporate ways of working.

In cases where the automation software project to be supplied by a dedicated automation system integration supplier covers multiple equipment vendors, it is particularly important that an integrated project delivery schedule is planned. The inclusion of a risk-based approach to validation, where customers are looking to leverage testing from equipment vendor locations to the overall validation life cycle, can present schedule challenges when supplying automation software components to the equipment vendor location. Equipment vendors that have strong automation software integration capabilities can often provide support that alleviates these challenges. This upfront planning helps to determine what can be achieved within the team, based on the different constraints and requirements for the overall project program. For an automation supplier to deliver on its commitments, the process inputs for the system must arrive in a timely manner. Often, though, there is a strain on key resources during the design phase of a project. Specifically, the team members with the most process knowledge are also involved in the equipment specification, equipment design review, and equipment testing. These activities run parallel to the automation project. If the automation supplier does not get the necessary information in time, challenges exist in providing the software to the equipment supplier for testing. Overall, incomplete requirements or assumptions on the supplier's or customer's part are always key gaps to close when engaging in project deliveries of any kind, and that is no different for automation.

Working with multiple vendors

When trying to integrate unit operations from multiple vendors into one central automation platform, there must be clear, unambiguous lines or boundaries in the scope of supply between each vendor. It is important to create software interface agreements that include a communication protocol with detailed requirements or parameters, so that each vendor knows what it is expected to provide to the other vendor. For example, if Vendor A wants to put a supervisory control and data acquisition (SCADA) system

Picture: rioloENIno/shutterstock.com

on top of Vendor B's programmable logic controllers (PLCs), Vendor A must know where any data blocks are and how the data is arranged. If Vendor A does not have this information and has to wait until the PLC project is finished before it can do its SCADA screens, it will likely miss the project deadline. It is possible to streamline this process by partnering with an equipment vendor that can also supply and integrate the software. This helps to eliminate silos that can exist in a multi-vendor approach, increasing communication and speed, and reducing potential confusion and errors. A partner with knowledge in both automation and process development not only understands what they are trying to automate but also has the foresight to recognize issues that could become major, and costly, roadblocks later.

Capacity expansion

New facilities are often designed based on the expected demand for a product. If that demand increases beyond the capacity of the facility, it is more than likely that there will be a need for additional equipment. This creates one of the biggest challenges of automation integration, which is to connect new equipment without interrupting current production. With capacity expansion for stainless steel, this can lead to restrictions in the ability to clean-in-place (CIP) or sterilisation-in-place (SIP) enough equipment with the current utility infrastructure. It can also lead to shortages from a water for injection (WFI) perspective, steam header pressure, or other utilities.

These issues and others related to stainless-steel equipment are, in some cases, being resolved by the use of single-use mobile equipment. While offering the ability to move equipment to different locations dependent on the production process flow requirements, single-use solutions also provide the ability to increase capacity by scaling out production and adding more equipment units to the facility. By using disposable bags, single-use equipment removes the need to cater for CIP and SIP of these units. With a growing need for production flexibility, this concept has encouraged a steady trend in biomanufacturing and offers sizable benefits when employed across multiple facilities with automation. In addition, advances in inline conditioning for chromatography skids are giving way to using buffer on demand, reducing the need for a large number of buffer vessels or buffer totes. Advances in continuous chromatography are also helping to achieve greater throughput in downstream processing.

Options for growth

When building for flexible production, you should be mindful of the small but important details of your facility design, such as locations for wiring and proper placement of communication and electrical outlets. Planning these details in advance allows you to reconfigure your facility later as needs change, which is critical in a mobile, single-use production facility. In addition, with future expansion and the need to connect more than one facility, is important to use consistent data models, in order to gather insight into what is happening across facilities. The more similar each automation product is or has the same type of batch context and taxonomy used within the software structure, the easier it is to collect and disseminate the information.

Finally, planning cannot stop with merely establishing the details on how to successfully execute your current capacity expansion and automation integration. One must also think ahead and consider how to maintain system performance, such as software upgrades and/or technical support after installation is complete, as well as future automation needs, such as add-ins. This can be accomplished by choosing a vendor that offers more than just a transactional relationship; this partner should be one that intends to play an active role in your long-term strategy by adding value throughout the expansion and beyond. ■

This article is an adaptation of What You Need To Know To Integrate Automation In Your Biomanufacturing Environment by Trevor Marshall, Zenith Technologies and Scott Mangiacotti, GE Healthcare Life Sciences, first published on BioProcess Online, August 24, 2018.

Reaching global markets

EARLY DRUG DEVELOPMENT Small- and medium-size European companies face the challenge of establishing global B2B activities in order to access relevant markets along the drug development value chain. YUMAB's flexible business model for the development of fully human antibodies attracts corporations overseas and facilitates international partnerships

› Dr. Thomas Schirrmann, CEO, YUMAB GmbH

Effective cooperation between small- and medium-sized enterprises (SMEs) along the drug development value chain can accelerate the process and can generate innovative candidates for novel therapies in areas of unmet medical needs. In particular, technical collaborations that bridge early phases in target identification and lead development promise a successful edge in global competition. However, most European biotech SMEs face the challenge of identifying and forging profitable international partnerships.

Providing bridging technologies

There is a constant need for technologies that identify and validate novel drug targets in a short period of time to accelerate bench to bed development. SMEs with a powerful, unique tech platform and a service-oriented business are preferred partners for these early stages. YUMAB GmbH is an expert in the development of fully-human antibodies closest to natural germline among those on the market. YUMAB antibodies combine maximum epitope diversity (library size →10^{11}) with minimal risk for immunogenicity. Thus, the YUMAB platform also provides access to difficult targets, like membrane-spanning proteins, and enables a de-risked clinical testing. First antibody candidates are identified within weeks, saving precious time for later development stages. YUMAB steadily builds a network with SME decision-makers at global, early drug development events.

A flexible, customer-oriented approach is crucial for successful partnerships. YUMAB's advanced, fully-human antibody platform is applicable to a broad therapeutic spectrum. Also, YUMAB can isolate most promising antibody candidates from patient groups with unique immune systems. The versatility of the technology enables engineered antibodies with adjustments in affinity, cross-activity, or stability – in diverse antibody formats.

Interlocking technologies and flexible business models facilitate global partnerships

Pictures: ©Shutterstock / Pogonici

Flexibility is key

The cooperation with US-based company RubrYc Therapeutics, Inc. supports this flexible approach: "Our industry is a leader in many aspects for international collaboration - discovery and development of many new medicines simply would not be possible without such collaboration. We have had a great experience collaborating with YUMAB, where complementary technologies and capabilities have been flexibly and efficiently deployed to reveal critical aspects of our approach to biotherapeutic discovery," said Isaac J. Bright, Co-Founder and CEO of RubrYc Therapeutics, Inc.

Another, often underestimated success factor is the proffering of accommodating business conditions. YUMAB grants attractive options to facilitate collaborations with SMEs and offers its human antibody platform in fee-for-service solutions. This model was key to YUMAB's fruitful collaboration with Singapore-based academic partners, which has resulted in the foundation of Enleofen Bio Pte. Ltd. With a novel antibody engineered by YUMAB, Enleofen focuses on the development of first-in-class immunotherapeutics for the treatment of fibrotic diseases by targeting interleukin-11. ■

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