Integration of Single Use Equipment:
Hybrid Technology and Automation

Abstract

The hybrid systems that are created by the combination of single-use (SU) systems and stainless steel technology offer a range of benefits in terms of process control. The efficient connection of SU equipment to a stainless steel backbone is particularly valuable in terms of clarity, operability, ergonomics and cleanability of the system. Special solutions for the automation of SU systems enable seamless integration into an existing automation environment. By means of hybrid technology, and intelligent automation strategies, the implementation of customer-specific standards is facilitated. The SU equipment, the stainless steel frame and the appropriate automation concept are thus combined to form a coherent entity. This integration yields real added value for process control.

Introduction

Single-use process technologies have been increasingly incorporated into the manufacturing of biopharmaceutical products over the past two decades. While the reasons for implementing SU systems for biomanufacturing are compelling, there are still some challenges and concerns related to their use. SU versus stainless steel – this discussion has been going on for many years. Each approach has its obvious advantages and drawbacks, but why should we have to decide for one and exclude the other? Why not combine the best of both worlds – single-use *and* stainless steel – and benefit from the resulting hybrid technology? Special solutions for intelligent automation, the design of a stainless steel "backbone" for SU systems and the efficient connection of equipment of all kinds enable seamless integration and thereby provide numerous advantages for process control.

The biopharmaceutical industry benefits from single-use technology – but is it really so much better than stainless steel? A reality check.

Many forces are driving the adoption of single-use technology in the biopharmaceutical industry, and this is especially true in multi-product facilities. Facilities that produce therapeutic substances for clinical trials, for example, must be able to manufacture a vast range of products in relatively small volumes. Single-use systems are commonly expected to allow a higher degree of flexibility, while stainless steel equipment often lacks that flexibility, but not necessarily in every case. Highly flexible stainless steel systems are available, from modular, mobile plug-and-play units through to super skid technology.

It goes without saying that cost is a very important factor. The investment cost for single-use equipment is lower. Some companies have managed to reduce CAPEX outlay for their new plants by up to 40% with the acquisition of this cost efficient technology. The time to market is another important aspect to be considered when planning a new facility. Single-use promises much faster

project realization, but delivery times of up to 25 weeks have been reported for certain single-use components, such as single-use bioreactors, during production. Naturally, the requirements for equipment cleaning and cleaning validation are reduced when disposables are used. This is not without advantages – cleaning and sterilization (CIP/SIP) are omitted in the single-use flow path – but in the industry currently, standardized utilities for trouble-free performance of CIP/SIP are available on a commercial scale and ensure an easy-to-handle cleaning procedure. [1],[2],[3]

The obvious drawbacks of single-use systems

What are the challenges and concerns related to the use of SU systems that remain after considering all their advantages? Ongoing operating costs are increased by the purchase and disposal of consumables. Leachable and extractable substances from the product-contact surfaces may contaminate the products. There is no satisfactory industrial design with consistent and uniform standards for the installation and use of SU production plants. Besides shortcomings in the documentation of SU systems, there is also a lack of regulatory experience with many single-use technologies.

Furthermore, the acquisition of single-use equipment is also associated with sourcing limitations. [4] Off-the-shelf products with one pre-determined design limit process flexibility. Many manual operations are necessary in plants featuring single-use equipment, which leads to higher error susceptibility. Suitable sensors for bioprocessing are lacking in disposable reactors, and another weak point is process automation. Automation islands are frequent phenomena with SU systems, and integrating the equipment in larger automation systems often entails difficulties. [1]

Integrative solutions for the automation of SU equipment

A number of suppliers offer single-use products on the market. For example, many of these suppliers provide a catalogue of bioreactors for which different configuration options are available. As far as software is concerned, however, in most cases one single solution is offered, which is based on the manufacturer's standard.

The situation is similar with measurement technology: each supplier relies on its own special system and is rarely flexible with regard to its own standard.

The customer usually has a need for a single, specific standard that applies to the operation of the entire plant and, at the same time, allows the integration of new equipment at any time without any problems. In the case of existing facilities, it is important to be able to maintain the established standard that applies there. This means that customized solutions adapted to the customer's requirements are called for when it comes to the integration of SU technology or equipment for measurement and sensor technology.

The low flexibility of the manufacturer's standard on the one hand, and the customer-specific requirements and conditions on the other hand, contradict each other to a certain degree. The solution consists of a uniform automation environment, with the potential for integration of any system, existing or newly acquired. If the customer has an existing automation infrastructure, further systems can be incorporated into the current environment. The standard systems of different manufacturers are modified accordingly and are integrated into the virtualized platform. The on-

site automation system, and all package units, are “taught” to speak the same language. With such an adaptation to customer-specific conditions and uniform standard, the familiar user interface and the accustomed method of operation can be retained. Last but not least, a uniform standard is also advantageous for a cost-effective and reasonable way of managing spare parts.

The spectrum of automation solutions ranges from the stand-alone solution, with standard software for the single-use area, to extensive process control systems in regulated environments. Customized solutions are developed based on the customer’s individual requirements using established methods of process automation. Standardized and modular functions are developed by these means which guarantee the highest degree of flexibility and production reliability. The structured setup of the automation software and the strict adherence to the GAMP guidelines guarantee the fulfilment of the high quality requirements demanded from production processes in a regulated environment.

The integration of measurement technology and other components, such as pumps, mass flow controllers for gases etc. is also possible, again using customer standards.

Figure 1: The control cabinet forms the "heart" of the automation system. It contains all the necessary hardware to connect the sensors and actuators on the one hand and to run the control software on the other. The control cabinet is also individually designed to meet customer-specific conditions and requirements.

Special software solutions for SU automation

Besides the hardware for integration in an existing environment, special integrative solutions for the software have been developed. In principle, any software system can serve as the basis for automation, regardless of the supplier. The PCS7 system from Siemens has a particularly strong presence in several European countries, with very sophisticated solutions having been developed based on the PCS7 software. A PCS7 standard solution, developed by ZETA in 2017, is using only standard features from the internal PCS7 library.

The PCS7 system is highly modular. A dedicated phase is built in SIMATIC Batch for each step in a sequence. The customer can change the sequence of the steps in the phase if, for example, the equipment changes or an adjustment is necessary, without requesting support from the automation

manufacturer. All modules in use, including Batch Manager, Recipe Creator, Alarm Management, Trending etc. are Siemens standard functions. Other systems programmed in PCS7 can easily be integrated into the PCS7 multi-project environment. Should an expansion of a bioreactor train be needed, integration of the additional new systems can be handled easily and quickly. Should assistance still be required, any automation manufacturer who can program PCS7 can be called on for support. Furthermore, the Siemens internal support can be used for requests. The PCS7 software is continuously maintained by Siemens. Hotfixes and security updates will also be available in the future. Virtualization is fully supported. Due to Siemens standard migration tools, an eventual change of the operating system is easy to manage and does not require requalification of the whole system. The software and its modular concept have been qualified according to the GAMP 5 guidelines.

Single-use – stainless steel hybrid plants: combining the best of two worlds

Hybrid technology integrates well-established stainless steel system standards and methods into SU solutions. By this approach, a move is made towards a dance floor concept in which process and handling performance are boosted by stainless steel support for intelligent clustering of the equipment. This leads to highly sophisticated hybrid plants for industrial production, which are interconnected and cross-functional. Well thought-out engineering concepts enable integrated production processes and guarantee a maximum of process reliability and reproducibility. Individually customized solutions are available for the integration of single-use equipment into existing production plants, the replacement of individual components, such as TCUs, gassing stations (optionally including certification according to 21CFR177, USP Class VI, 3.1) and agitator drives, as well as the planning and construction of peripheral stainless steel pipes and equipment. Existing infrastructure and media supply can be made available for single-use technology. Hybrid systems are considered a further development of single-use technology and pave the way for production according to GMP standards.

ZETA's concept of SU integration: customized and independent of the supplier

Companies such as Cytiva, Merck-Millipore, Sartorius, ThermoFisher or Pall offer a broad range of equipment for single-use applications. All suppliers have their own product designs and specifications, which can lead to difficulties when the plan is to combine them or exchange one for the other. To achieve smooth integration a stainless steel "backbone" is constructed, which might consist of adequate platforms, piping and conduits, or a routing system for piping, plus multi-scale TCUs and gassing stations. This backbone is capable of receiving different pieces of SU equipment, even from different suppliers. This concept makes the connection of single-use bioreactors from 50 L to 2,000 L possible. Furthermore, bagtainers and bags from different suppliers can be used, with volumes from a few milliliters up to 5000 L. With this approach, well-known automation systems from Siemens, Rockwell or Emerson can be employed to integrate the single-use plant seamlessly into the existing automation environment. The familiar "look and feel" stays the same for the operator, which reduces handling complexity.

Ballroom and dance floor: production concepts of the future

"Facility of the Future" is the term to describe future production concepts that include the full application of single-use technologies. One of the emerging layout concepts is the ballroom concept. According to the original definition of that term from cleanroom technology, it is "a large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems." [5] Similar to a ballroom, the cleanroom is equipped flexibly with devices, depending on the process. This concept includes placing the bioprocess equipment on wheels, rather than in permanently fixed positions. Equipment is deployed flexibly by simply wheeling in and connecting additional operational units to meet the needs of a specific process, or multiple processes are run in a single space.

A modification of the ballroom application, where the ballroom does not have to be a single large space, has come to be known as the "dance floor concept". In this layout concept, the equipment can be distributed over adjacent smaller spaces that would be linked by through-the-wall connections. By these means the process remains closed. The dance floor approach enables application of the ballroom concept in existing facilities with minimal modification. [6],[7] Implementing the dance floor concept,when generating stainless steel support for intelligent clustering of equipment, is conceived as an interesting option to create facilities of the future.

Environment, health and safety: stainless steel backbone brings a clear improvement

Stainless steel structures for the efficient arrangement of the equipment offer clear advantages in terms of environment, health and safety (EHS) during plant operation. Work platforms and stairways are designed to fit perfectly into limited spaces and provide easy access for equipment handling and maintenance. The numerous cables and hoses, which are characteristic for single-use applications, are routed through stainless steel supports and fixed along the framework and under the platforms. This minimizes the overall length of the hoses required and also prevents them from kinking.

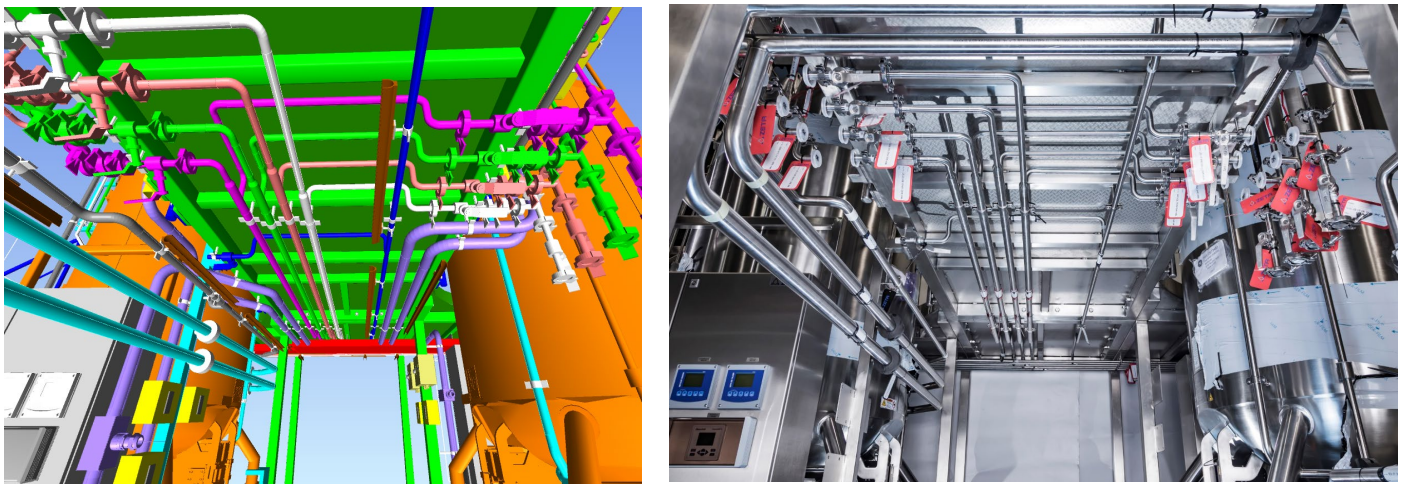

Figure 2: Gas pipings and conduits fixed under a work platform.

The result is an enormous improvement in clarity, operability, ergonomics and cleanability, and a reduction in operating errors. Utility stations and pipelines made of stainless steel for media supply are also a means for the efficient and flexible design of hybrid systems. Additional equipment such as floor scales, pump stations, gassing stations and measuring devices, including temperature

control units (TCUs), are integrated into the hybrid system and connected to the automation environment.

Single-use bioreactor integration: a ZETA project which demonstrates the successful implementation of hybrid technology

ZETA successfully implemented a project involving the integration of single-use process equipment into a stainless steel plant for a customer in Switzerland in 2018. It included engineering, manufacturing and installation of a stainless steel work platform with utility supply piping for the clean rooms as well as automation, based on Siemens PCS7, of the single-use bioreactors. The single-use equipment, delivered by the supplier, consisted of four single-use bioreactors (50, 500 and2,000L). Starting from basic and detail design, the project scope covered a large section of the ZETA project life cycle, including static and dynamic FAT for the bioreactors, including the bags and the platform, delivery, electrical and mechanical installation, programming, commissioning and qualification. Complete documentation was FDA & GMP compliant.

Figure 3: Stainless steel platform for integration of four single-use bioreactors.

As time to market was key, the bioreactor trains including platforms and automation were completed in only six months, process validation was fully established after ten months. It goes without saying that the ZETA team faced and overcame numerous challenges in a project of such complexity. With the aid of 3D modelling, standalone single-use and auxiliary systems were integrated into the plant and a space-saving design for conduits, piping and tubing was developed. Process reliability was significantly improved thanks to the tube routing. Tube kinking problems during operation and tripping hazards were removed. The EHS aspect was improved greatly by these measures. The tube lengths necessary for single-use systems were minimized by the use of stainless steel piping.

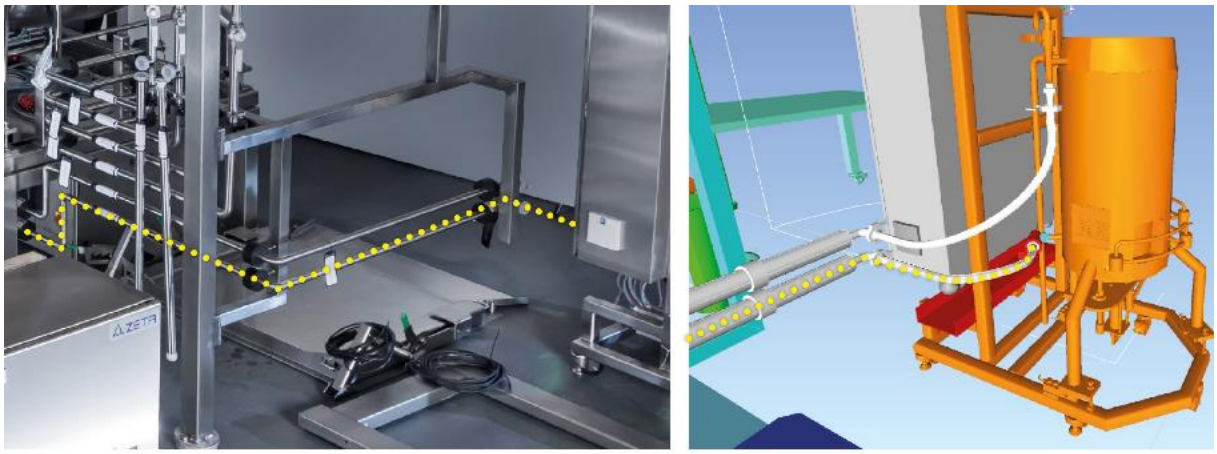

Figure 4: Supports made of stainless steel or plastic allow optimal guidance of hoses and cables.

The plant was designed to ensure easy cleanability and maintenance, plus ergonomic access to the SU equipment. Static and dynamic tests were performed at the ZETA workshop to ensure functionality. Moreover, ZETA also provided an efficient solution for automation, allowing a flexible process. The hardware and software for automation were designed for integration into an existing environment and delivered ready to use.

ZETA's cooperation with Lonza results in hybrid solutions for multi-purpose plant

The stainless steel backbone for another ambitious hybrid technology project consists of 6.2 km length of piping, 29 utility stations, various stainless steel platforms and scale skids. The complex multi-purpose plant, which is designed for the utmost flexibility to map a wide range of processes at different scales, is part of Ibex™ Solutions, Lonza's new Biopark in Visp (Switzerland).

ZETA provided the detailed layout, successfully integrating upstream, midstream and downstream processes in a single module. Based on the P&IDs, a 3D model was designed that ensured a space-saving design to meet the requirements for the limited area available. Various media needed to be provided for different processes and were distributed via the utility stations to six rooms.[8]

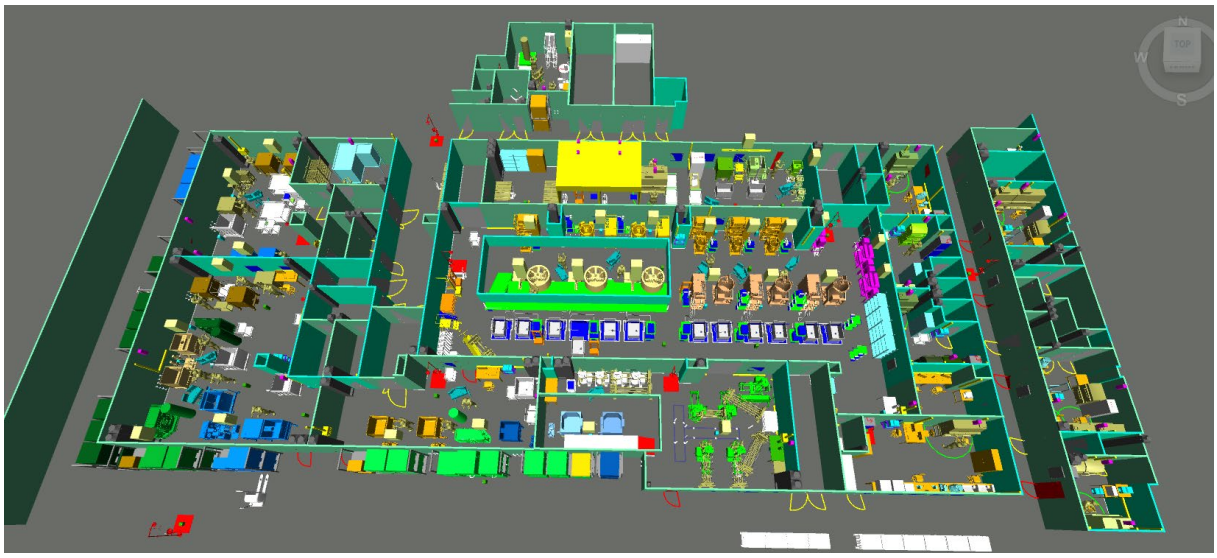

Figure 5: 3D-Model of hybrid multipurpose plant

Conclusion

For many years now, biopharmaceutical production has made increasing use of disposable equipment. SU components are easier to handle, do not require cleaning validation and are therefore cost-effective. On the other hand, SU components are highly standardized, which becomes a problem if the plant operator is seeking specific production solutions. SU bioreactors are only available in standard sizes, and the length and number of pipelines are also standardized. Deviations in a standardized process result in higher costs and delays, due to the additional necessary risk assessments and qualification processes, in order to continue to be in compliance with GMP regulations. In contrast, stainless steel components are much more robust and allow better process monitoring. There are promising approaches to benefit from the advantages of both systems in the context of hybrid solutions. Such hybrid systems originate from engineering concepts that intelligently combine SU technology with conventional stainless steel components. The advantages of both process systems come into play: high flexibility and reduced set-up times of the SU technology meet robust stainless steel components that better withstand typical process conditions, e.g. high pressures and temperatures, and can be easily automated. The results are improvements in process reliability and reproducibility. For the integration of the process equipment into the existing automation environment, there are intelligent automation solutions that are based on the user's standard software. The SU equipment, the stainless steel frame and the appropriate automation concept are thus combined to form a larger, fully-integrated facility which represents real added value for process control.

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References

[1] SUT Poster Hybrid Systems, ZETA Symposium 2019

[2] Hodge, G 2004. Disposable Components Enable a New Approach to Biopharmaceutical Manufacturing. BioPharm Int. 17:38-49.

[3] Fromison, J 2009. Disposables in Clinical Manufacturing. Am. Pharmaceut. Rev. 12:20-27.

[4] Levine, H.L., Stock, R., Hummel, H., Jones S.D.; Efficient, Flexible Facilities for the 21st Century; BioProcessing International, Dec 1, 2012

[5] Pharmaceutical Engineers (ISPE) Baseline Guide: Volume 6 - Biopharmaceutical Manufacturing Facilities (2013)

[6] Page, T., Galliher P.; Dancing In The Bioprocessing Ballroom: Voices Of Experience; Bioprocess Online Article, Dec. 7, 2018

[7] Badertscher B, Eibl R, Eibl D. Single-Use Technologie von A-Z. DECHEMA [Internet]. 2017; Available from: http://a-z-single-use.org

[8] Press Release: ZETA Engineering for LONZA mega project Ibex Solutions, Dec. 2019 Available from: https://www.zeta.com/lonza-erweitert-mit-ibextmsolutions-seinen-biopark_165_40.htm