

Pharmaceutical Technology®

A Look at 30 Years of Change in Pharmaceutical Automation

Bob Lenich and Christie Deitz

Automation took hold gradually in the life-science industry. Its adoption brought the industry innovations and improved efficiency. Recent years witnessed the emergence of batch-automation systems and the development of standards for automation. The authors discuss the major changes automation brought to the industry and examine the rapid pace of technological development.

Bob Lenich* is life science strategic business director at Emerson Process Management, 12301 Research Blvd., Austin, TX 78759, tel. 512.834.7033, fax 512.832.3199, bob.lenich@emersonprocess.com. **Christie Deitz** is a senior principal engineer in the Emerson Life Sciences Industry Center.

*To whom all correspondence should be addressed.

Where were you 30 years ago?

Bob: "I had just graduated from high school and was working as a CO-OP at Cabot before going to college at Rose Hulman Institute of Technology." Christie: "I was a kid enjoying a carefree summer."

Although automation has taken hold slowly in the life sciences, it has come to play an increasingly important role in keeping the drug industry moving ahead. While other industries such as general chemicals and specialty chemicals consistently moved to apply new technologies and improve manufacturing performance, the life-science industry lagged behind. But in the past few years, the pace of innovation has accelerated greatly, and it shows no sign of slowing down. This article will look at major automation trends in the life-science field from 1977 to the present and provide ideas about possible developments in the years to come.

The old days (pre-1977)

The first programmable logic controller (PLC) debuted in 1969, but its widespread use in the pharmaceutical industry was still years, if not decades away. Channel-based analog equipment was the standard. Single controls—either pneumatic or electronic—were mounted on walls in big racks. Little, if any, data were recorded by means other than manual recordkeeping, which was performed on paper by operators. Circular chart recorders and strip chart recorders were the main way of recording process parameters.

The late 1970s and early 1980s

The first distributed control systems (DCSs) emerged in 1975, and they were used mostly in the chemical industry at first. DCS gained popularity in the life-science industries in the latter part of the decade and in the early 1980s. The US Food and Drug



A few thoughts on choosing an automation vendor

The past 30 years brought many changes to the life-science automation environment. The pace of changes is accelerating. Choosing the right automation partner is increasingly important as automation and information management become more critical to life-science manufacturing and operations. An automation supplier should be financially strong and robust. Because the pace of technology change continues to accelerate, it's vital to have a supplier who will be able to support investment over time. An automation supplier should also be global. This characteristic supports the establishment of almost identical plants around the world and allows clients to relocate manufacturing at will. Finally, an automation partner must have the experience and technical wherewithal to strike a balance between delivering leading-edge solutions and respecting the conservative nature of most life-science companies.

Administration was ramping up its regulatory requirements, and automation was seen as a good tool to facilitate compliance. The pursuit of automation accelerated when batch-control automation and batch-unit operations control became available in 1983. The ability to use configurable, off-the-shelf (OTS) software to write sequences, take automatic actions based on failure, create recipes, and synchronize parallel-unit operations delivered significant improvements to life-science manufacturing. Implementing automation was a large, challenging task because control rooms and wiring were centralized. Every-

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1995. The Good Automated Manufacturing Practice (GAMP) Forum issued *The GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture*. GAMP became the user community's forum for comments and responses to governmental regulations. Automation users formed the group in the United Kingdom in 1991 to provide practical standards for validating automation systems.

thing was linked to a combination of a main control room and a massive main wiring hub. Thinking about batch software logic and failure handling was new to many people.

Through the second half of the 1980s, new technology appeared and eclipsed the previously dominant DCSes. Custom-built DCSes were replaced by commercial OTS systems, which were much less expensive. New products fostered an aggressive move away from customized hardware development to standard common OTS products using Ethernet communications.

The late 1980s and early 1990s

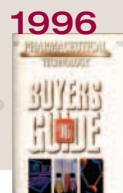
Once people gained experience automating batches, batch

The goal of batch standards was for everyone to talk the same language, use well defined terms, and share a common architecture.

standards began to be developed. The goal was for everyone to talk the same language, use well defined terms, and share a common architecture. The first batch automation standard, S88 (on which work had begun in 1988), was approved by the Instrument Society of America in 1995. S88 was initially implemented in two applications, PID's "Open Batch" real-time batch-recipe execution service and Consilium's "Director" manufacturing execution system. These applications became the basis for many of the batch-automation solutions that developed around the S88 standard. In addition, the World Batch Forum was founded in 1994. This forum for the batch-process industries focuses on best practices for automating and applying technology to batch manufacturing.

By the mid 1990s, several product platforms built on these new standards began to appear. The concepts of class-based configuration software were developed. Class-based software facilitated the establishment of common libraries of building-block modules linked to unique instances of the modules as they are applied. The library modules were then quickly replicated, but change control could also easily be applied. Because the various instances can maintain the characteristics of their class, it was easy to change them and document the change. Although not initially applied to their full extent, these concepts enabled the modular construction approach used by most life-science companies in the early 2000s.

In addition to automation standards, regulatory concerns arose involving system management, production automation, and the data being created. In response to the uncertainty about validating computer systems, end users, automation vendors, and consultants collaborated to define and standardize practices. In 1994, the Parenteral Drug Association (PDA) issued *Technical Report 18: Validation of Computer-Related Systems*. In 1995, the Good Automated Manufacturing Practice (GAMP) Forum issued *The GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture*. GAMP became the user community's forum for comments and responses to governmental regulations. Also, PDA issued *Technical Report 32* to define good practices for



auditing suppliers. Although 21 CFR Part 11 was not formally issued until 1997, it had begun to be developed in the early 1990s. Part 11 focused on how to design, implement, test, and manage change with automation systems and the electronic data created. By the late 1990s, the focus had clearly begun to shift from applying technology to managing records and demonstrating regulatory compliance.

The late 1990s and early 2000s

The standardization movement gained momentum with the advent of the new century. Life-sciences companies built upon trends from the early 1990s by using distributed hardware and putting Ethernet-enabled input-output in the field. These measures were followed into the field by controllers and their cabinets as centralized rack rooms were superseded. Yet, life-science companies proved quite conservative when it came to adopting the digital field buses that were becoming common in other industries. These companies are only now moving in this direction.

Life-science industry users also accelerated their demand

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2004. The US Food and Drug Administration published *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach* in 2004. The policy encouraged life-science companies to pursue innovation and weigh risk when seeking methods to improve manufacturing processes. Companies began to adopt technology such as digital buses, multivariable process control, and embedded in-line analytical analysis.

for standardized, configurable, OTS equipment. They also began demanding standardized connections between software applications. In the real-time world, standards such as OPC for Process Control (OPC) became the accepted means to share data between plant-floor applications.

Yet more real-time connectivity for batch information was needed, so the industry participated in the development of the S95 standard to help define connections between applications such as enterprise-resource planning and plant-floor automation systems (e.g., DCS) to make batch execution and recipe management more effective. Recipe- and materials-management applications, their interaction, and their connectivity were key for life-science users.

The regulatory burden peaked at the turn of the century. Restrictive audit findings by FDA (which increased the burden of rules already on the books) and the more general year-2000 computer issues led life-science companies to focus on

meeting regulations, not on improving manufacturing. Companies used GAMP and other industry avenues to warn regulatory bodies of their heavy burdens.

Regulations such as Part 11, however, also drove the life-science industry to move to the forefront in some areas. Today, life-science companies are ahead of chemical and other in-

Inspired by FDA, companies are increasing the integration of their control system and their various enterprise systems.

dustries on the issues of data security, record security, lot tracking, and batch management in general. Not only did fear of Part 11 enforcement inspire the industry to take action, but the regulation's focus on electronic data and record issues caused companies to reevaluate and modify their systems even when enforcement lessened. Also, life-sciences vendors were motivated to improve product features for electronic data and records.

Recent changes

In response to the industry's concerns, FDA released its report titled *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach* in 2004. FDA's new policy allowed life-science companies to be innovative and to apply risk-based technology approaches to improve manufacturing. As a result, the adoption of digital buses, advanced control technology such as neural nets and multivariable process control, and embedded in-line analytical analysis is becoming widespread.

Further extensions of the standards movement include completely modularized plant construction and the accelerated use of standardized skid-mounted equipment. These changes made the construction process faster. Combined with the spread of standards and class-based approaches, they have had a significant effect on automation and technology. Standardized process equipment spurred the use of commercial, OTS hardware for networking, computing, and user interfacing. This hardware makes support easier to deliver and accelerates the technology change life-science companies face.

Also significant is the increased use of operational excellence programs such as "OpX." When life-science companies examined automation in the 1970s or early 1980s, their risk-adversion and lack of incentives to optimize manufacturing meant



they only relied on techniques that had already been proven. This has clearly changed. The business is more competitive, customers are increasingly price-conscious, and manufacturing and supply-chain efficiency is more important. The plant floor and production are now tied to the way laboratories work, to the timely release of new products, and to overall profitability. Putting the right kind of automation platform in place can help reach these goals.

Operational excellence also has accelerated companies' top-to-bottom integration. Because FDA now allows more flexibility in approaches to automation, companies are increasing the integration of their control system and their various enterprise systems. The OpX program also encourages the

change from paper-based compliance systems to electronic records and will continue to change how life-science companies optimize unit operations, manufacturing, product approval, and product release.

Another big trend is flexibility. The industry is moving from what had been organic-based synthesis and organic-based products to biologic products. Biologics are more complex, but they're also targeted at smaller groups and even individuals. They require significantly more flexibility on the part of a manufacturer. Manufacturing-execution systems integrated with process-control systems will become the platform for flexibility, optimization, and compliance. **PT**

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