Standardization and Certification Challenges for Biopharmaceutical Plants

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With automation and globalization come a variety of issues that affect manufacturing decisions concerning standardization, certification, and regulatory validation. The biopharmaceutical industry faces challenges related to the automation process’s unseen operational costs.

Bioprocessing—a technique that produces biological material, such as genetically engineered microbial strains and commercially useful chemicals—is big business in the US and growing quickly around the world. An increasing number of pharmaceuticals are now manufactured using bioprocessing techniques. Quality control of these products is a huge issue.

Bioprocessing (and the pharmaceutical industry in general) is highly regulated. The groups that develop guidelines, standards, certifications, validations, and so on aim to ensure extremely high quality levels from the manufacturing plants’ pipes, tanks, and valves all the way through the finished product, with a focus on cleanability, sterility, and reproducibility.

However, in the past 10 or so years, the industry has been pushing for increased plant efficiency and manufacturing globalization, and is now focusing on plant automation. The groups involved in standardization, certification, and validation have been working hard to keep up with the industry’s needs and stay in sync. A brief discussion of these organizations with some history gives additional perspective on the current state of biopharmaceutical plant standards and regulation.
OVERVIEW OF THE ORGANIZATIONS
Figure 1 depicts the purview of the groups that influence biopharmaceutical guidelines, standards, and regulations. The influential agents (ovals)—Bio-process Systems Alliance (BPSA)/BioPhorum Operations Group (BPOG), American Society of Mechanical Engineers Bioprocessing Equipment Group (ASME-BPE), International Society for Pharmaceutical Engineering (ISPE), and US Food and Drug Administration (FDA)—cover different levels of the plant and manufacturing process. Suppliers, distributors, and drug manufacturers involved with development of each component, piece of equipment, or drug are listed above their area of interest. (This figure is based on a diagram by Jerry Martin, Pall Life Sciences, chairman BPSA.)

The more that these national bodies can use internationally recognized standards, the fewer the hurdles that biopharmaceutical plants operating globally must overcome.

The Bio-process Systems Alliance (BPSA), formed in 2005, is a trade association that pushes single-use (disposable) materials used in plants, such as bags, filtration products, and connectors. The BioPhorum Operations Group (BPOG), another trade group, covers all types of components and equipment. Both groups support their members as the industry changes and are involved with creating standards and best practices.

The American Society of Mechanical Engineers Bioprocessing Equipment Group (ASME-BPE) maintains the official ANSI international standard developed for biopharmaceutical manufacturing equipment design and construction.

The International Society for Pharmaceutical Engineering (ISPE) focuses on facilitating communication between the pharmaceutical industry and regulators to develop quality standards; its work butt’s up against several International Organization for Standardization (ISO) areas.

And there’s the FDA, which covers drug manufacturing processes, product quality, and distribution to customers. The FDA must validate and approve the manufacturing process before production begins and requires that each drug batch be tested for quality during manufacturing. Multiple samples are taken, tested, and documented throughout the process. If there’s any variation in the expected quality, the product is pulled.


Because the US government asks its agencies to use consensus-based standards rather than create regulations, the FDA typically relies on recognized standards-developing organizations (SDOs), such as the ASME, ISPE, ISO, and IEEE, to define the standards, and then uses those. The reason it can feel as though the FDA’s control is everywhere is because each time something
changes in a plant, such as the material of a seal or the type of component that takes a sample, the FDA requires either partial revalidation or revalidation of the entire manufacturing process. In essence, it requires that the manufacturer revalidate that the product will retain its purity and efficacy. Each validation can cost more than $100,000, and for some products, the time lost waiting to restart a plant after validation can result in millions of dollars in losses. It’s this reason that change—no matter how much of an improvement—is often resisted after a plant starts running.

**BIOPHARMACEUTICAL STANDARDS AND CERTIFICATIONS: HOW DID WE GET HERE?**

In 1989, an ad hoc committee on bioprocessing equipment was established to create a standard for bioprocessing equipment. The committee began by creating guidelines that covered the mechanical portion of bioprocessing in factories, specifying how to best design and build equipment used in biopharmaceuticals production. This standard was originally a set of best practices designed to ensure both manufacturing safety and consistent product quality and purity.

In the mid-1990s, ASME stepped in and requested that the guidelines be turned into a true set of standards that it could adopt, and in 1997, the first edition of the ASME-BPE standard was approved and published. This standard, although very thorough and well regarded, hasn’t been universally adopted. Many countries or regions have their own standards, which causes significant issues for companies that want to use the same factory equipment, design, and processes in multiple global locations. Internationalization issues, with respect to language, measurements, and needs, consistently push the groups to reassess and modify the ASME-BPE standard. But this issue isn’t the main thrust of the story.

For the past 10 years, the ASME-BPE has been working on a certification process for all components used to construct biopharmaceutical plants. The effort is designed to prevent plant builders from purchasing substandard parts from new manufacturers around the world. The effort started with simple parts, such as tubing and fittings, and is currently focusing on bioreactors and chromatography skids that will allow for continuous monitoring of product quality. In addition, the manufacturing process is moving from discrete batches to a continuous flow of product.

There’s significant controversy concerning automation of pharmaceutical plants, as Cheryl Scott and Lorna McLeod point out:

*What used to be a personnel-operated and -managed process is becoming run by automated software.*

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Often the point is made that making drugs (especially biologics) is too complicated to automate, that the regulatory requirements get in the way. [Christopher Procyshyn, chief executive officer of Vanrx PharmaSystems] counters: “We can’t make cars that kill people, either.” The larger difference, he says, is in cost pressures and efficiencies. “With more pressures from global healthcare peers now,” he said, “we are seeing automation take hold. People want to put more into their R&D, and automation saves money. It doesn’t cost more if it’s done properly.”

Although automation is being adopted more slowly than other industries due to a general fear of walking away and letting the control software take over, the cost of errors for some organizations is just too high. Automation’s upside, especially in aseptic processing, is that you prevent as much human intervention as possible to avoid contamination. But remember, each time a drug manufacturer makes a major change of this kind, it must revalidate the process with the FDA.

**AUTOMATION SOFTWARE**

Some more sophisticated plants are using commercial products like Rockwell
A software product was certified according to some standard, could pharmaceutical plants get by without customizing the standard commercial controlling software for their own plants? Scott and McLeod report from an interview with Martin Rhiel of Novatis that it likely isn’t that simple:²

It would be really nice to just buy it and implement it, but this doesn’t always work. In my personal opinion, a big hurdle is the regulatory environment. If you have a registered [validated] process, it’s difficult to change it, so that’s a big hurdle. Of course, there are cost pressures. Changing and revalidating a process and getting approval again, that’s a huge cost. So it was easy to use common technology that works well enough with the health authorities, and it was easier to get approval. If you’re at the forefront [of automation] and going to the health authority, it’s always difficult. But nowadays, the FDA is working together with pharmaceutical companies in implementing new technologies.

The answers aren’t obvious. However, it’s clear that biopharmaceutical plant automation will continue. When control systems—software or electronics—are altered, careful testing must be performed, because as many of us have experienced from software updates in less critical situations, they don’t always go as planned. The cost of “mistakes” in this arena is high.

REFERENCES

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