What's driving the need to revise ASME's bioprocess engineering standard after only two years? Progress—and the desire for better quality control. By Jeffrey Winters, Associate Editor

TURNA ROUND

To Michelle Gonzalez, a biopharmaceutical engineering consultant based in Thousand Oaks, Calif., the bioprocessing equipment standard is not a cold, technical document. It's personal.

"My mom benefited from the progress of the pharmaceutical industry," Gonzalez said. "More than 20 years ago, I worked in the most up-to-date facility that Genentech had for producing tPA"—a clot-busting drug used to treat heart attack patients. "That drug wound up saving my mom's life."

Gonzalez feels strongly about setting the highest standards for bioprocessing. That passion has been useful as she has worked on the latest ASME Bioprocessing Equipment Standard—the third such document in five years. The BPE is now on a two-year cycle to keep up with an industry that is racing ahead.

Indeed, with three meetings a year and a new edition about to hit the bookshelves, it's fair to say that the bioprocessing equipment standard is changing as fast as possible. And that's a good thing, according to Gonzalez.

"It's a rapidly evolving industry, so we need a living document," she said.

The stakes are increasingly higher, as biotechnology becomes a larger industry, ranging from pharmaceutical manufacturing to burgeoning fields such as bio-fuel production.

The core of bioprocess engineering is one of the most sensitive in all of manufacturing. Unlike pressure vessels or micromachines which, for all their complexity, have characteristics that are straightforward to predict as conditions change, bioprocesses—industrial-scale procedures that rely upon the activity of living organisms—can sometimes have minuscule tolerances. Let the temperature rise a little bit or allow the pH to drop, and instead of microbes producing a medicine, you have useless goo.

ASME first organized a group to look into bioprocessing in the late 1980s, when the biotech industry first began to take off. Within a decade, the field had developed so much that it was felt a standard was needed to help guide manufacturers to the best available practices.

The standard was most recently updated in 2005 and that edition reflected input from European and Asian engineers, not just American ones. It was part of an effort to make the ASME Bioprocessing Equipment Standard the *de facto* global benchmark by which all others would be measured.

'A RATHER NEW STANDARD'

With so much work put into that last standard, why is it being overhauled just two years later? Part of it is the standard's own success, suggested Jay Ankers, director of mechanical processing at LifeTek, a biotech firm in Plymouth Meeting, Pa. The more hands the standard falls into, the more requests there are for new areas to be included. In fact, Ankers said, the standard is now being written in a way that makes it easier to expand.

"Since the BPE is a rather new standard, some of the descriptions need to be clarified or amended based on feedback from actual application," added Sei Murakami of Hitachi Plant Technologies in Tokyo. For instance, many of the drawings in the standard have been revised to better match existing setups.

According to a market research survey, biotechnology is now a $35 billion business, and biopharmaceuticals are growing at a 13 percent annual rate. All that growth brings the inevitable growing pains. New facilities are built; old ones are expanded, and unfamiliar equipment becomes the link between profits and losses. According to the Census Bureau, drug manufacturers spent more than $6 billion in capital costs in 2005, and the pace is not slowing. In an environment that is so competitive, it's little wonder that engineers want expanded standards.

To get an edge on costs, for instance, manufacturers are looking to new suppliers, especially those in Asia, for various fittings. And with the cost of a material such as titanium up by a factor of 10, according to some estimates, that's not an insignificant issue. But when material is coming from unknown sources at an overseas location, quality can become compromised.

"Everybody has heard about the toys with lead paint imported from China," said Ankers. "But at the same time that was in the news, we got stainless steel castings from China that were inferior and titanium tubes, also from China, where 100 percent of them were splitting.

"If I bought the same dimensional tube from a U.S. or Japanese supplier—it's aircraft grade—you could build a nuclear reactor with it."

Also, suppliers can deliver widely different materials, all with the same name. "You buy a material such as EPDM and there can be 20 different varieties all with the same name," Ankers said. "Forget China and India. There are 20 different kinds just within the U.S. No one's going to standardize unless the end user demands it."

Such concerns are beginning to make their way into the BPE standard, as committee members push for a higher level of material purity. It's better, after all, to have 20 potential suppliers producing identical parts that can meet your need than to have just one or two. But setting a high standard is no guarantee that you'll be getting what you've ordered, Gonzalez said.

"We can bury ourselves with paper," Gonzalez said. "But that by itself won't keep fraud from occurring."

BEST POSSIBLE PRACTICES

Gonzalez thinks that it's more important to incorporate the best possible practices into the standard, ones that are backed by science, not custom. One instance where best practices don't match with science, Gonzalez said, is in the treatment of rust, also known as "rouge."

"People react with a great deal of anxiety when they see rust in stainless steel," Gonzalez said. "It's just iron, and nobody has died of an overdose of iron, unless you are hit over the head with a bar." Except in cases where cosmetics are being produced, she added, there's likely no reason to be overly concerned with a patina of rust on stainless steel parts.

More threatening, given the nature of bioprocessing, is the presence of a layer of bacteria on equipment. Gonzalez said a new task group was recently created to look at how the standard ought to deal with biofilms such as these. "People don't see it," she said. "You could have a very shiny surface with a thick coating of biofilm."

One reason why the standard up to now has not dealt more forcefully with the problem of biofilm is that the focus has been on new systems. "Once you have a new system on line, it's no longer new," Gonzalez said. "We need to start addressing maintenance in more depth."

Another area the standard has begun to address is that of legacy standards—instances in which common practices have been included in the standard, even though they may not be the best possible procedure. Gonzalez said one such issue being addressed in the standard is that of clean-in-place processes, which enable equipment to be flushed out automatically between batches. More than 40 years ago, Gonzalez said, a rule of thumb for the minimum flow needed to do this was agreed to: five feet per second. That's been the flow most manufacturers have adhered to since.

"But that's nonsense," Gonzalez said. "Flows change due to viscosity, temperature, pressure—a whole number of factors." Instead, Gonzalez feels a standard based on hydrodynamics, which could better anticipate the way a scouring turbulence could be induced in the flowing liquid, would be more useful in ensuring that machinery gets properly cleaned.

Another issue is adding design data to the standard, says Gerhard Kröhnert, a Germany-based consultant formerly with Dockweiler AG. Kröhnert said certain types of clamps were being produced with widely varying designs. "Nearly every manufacturer kept design data a secret," Kröhnert said. "The products weren't meeting the proper dimensions. At the end, it was obvious that systems were not interchangeable between manufacturers."

An obvious solution, Kröhnert said, would have been to adopt existing standards into the BPE, but that effort met resistance from American manufacturers. Instead, the various proprietary data was compiled into a table that was added into the 2005 standard. That solution, Kröhnert said, turned out to not go far enough. "It was just a compromise," he said. The subcommittee tasked with looking into the problem is moving toward a fully interchangeable standard—the first ever for clamps.

It's likely we are still far from the end of this era of rapid changes in the bioprocessing equipment standard. "Once you address and standardize something like tubing fittings," Ankers said, "the focus changes to the next thing that's causing problems."

And there's not a little altruism driving the process. "Our mission is thinking about how to make life better for the population of the world," Gonzalez said. ■