Manufacturing processes using living organisms have been around as long as civilization, and probably longer. You need live yeast, for instance, to make bread or beer. But it was a new idea in the early 1980s to run a factory making products that used living, often genetically modified organisms as part of the process feedstock to turn out bulk pharmaceuticals. As recently as twenty years ago, the bioprocessing industry didn’t have its own specialized machinery. According to Tony Cirillo of Jacobs Engineering, one of pioneers of the industry, bioprocessing plants originally used equipment designed for handling milk in dairies—effective, yes, but not as sophisticated as the industry wanted to become. Indeed, the bioprocess industry was so new that no one had a complete idea of what additional equipment features to specify.

That’s why in 1989, Cirillo and others in the industry got together under the aegis of ASME Codes and Standards to form the Bioprocessing Equipment Committee. The committee issued its first standard for bioprocessing equipment in 1997, and in a few weeks the group will publish the fifth edition of the standard, BPE-2009.

The standard covers the design, installation, and inspection of the equipment used in the bioprocessing and pharmaceutical industries—pumps, tubing, pressure vessels, tanks, and so forth.

The 2009 edition is an expansion on the previous edition in a number of areas. Two entire new parts have been added, addressing metals used in construction and certification of tubing and fitting manufacturers. New material also has been added throughout, including many sections and new appendices.

As with all codes and standards, the purpose of the BPE is to assure the integrity of the equipment and the products the equipment will make, and at the same time to put the least practical burden and cost on industry.

The BPE is an American National Standard that by 2002 had become an adopted international standard referenced in 29 countries. Use of the BPE Standard has continued to grow to the point that virtually all new biopharmaceutical plants in the United States and in many foreign countries have been designed to its requirements, or have retroactively incorporated the requirements.

**TWO NEW PARTS**

Among the larger changes in the new edition, is the new Part CR Certification. Until now, manufacturers of tubing and fittings marked their products with the letters “BPE” to indicate that the components met the requirements for material composition, dimensions, tolerances, welding and fabrication, surface finish, examination and inspection, and other details outlined in the BPE Standard. Intended initially as a self-policing method of identifying compliant products, there was no controlled assurance guaranteeing that components so marked actually met all of the BPE requirements. Part CR begins to establish those controls.

In the 2009 edition of the BPE, Part CR is limited to tub-
ing and fittings. Part CR establishes a method to confirm that a manufacturer’s tubing and fittings are BPE compliant and also provides authorization to approved organizations to mark components with the ASME BPE Symbol Stamp.

The certification process consists of five basic steps in the process:

1. An applicant for certification begins by developing a Quality Management System manual, which addresses all the processes, as outlined in literature provided by the BPE, to ensure that all applicable requirements of the current standard are met, and to identify any potential weak spots in a manufacturing operation.

2. When the manual is complete, the applicant applies to ASME Conformity Assessment for certification.

3. An ASME assigned survey team visits the facility or facilities of the applicant organization. The team will review the Quality Management System manual, the company’s manufacturing process, quality assurance process, documentation, product handling, and final quality of manufactured equipment.

4. A survey report is submitted to the BPE Certification Subcommittee, which will review the team’s findings and will vote on the application for certification in closed session.

5. When the BPE Certification Subcommittee has determined that an organization can meet all the requirements of the standard, the company receives a Certificate of Authorization. Periodic audits will be performed by an ASME audit team for the life of the certificate.

Another new part of the standard, Part MMOC Metallic Materials of Construction, was developed to identify metals commonly used in hygienic service and to set for these materials appropriate testing standards, mechanical and chemical properties, surface finish, fabrication guidelines, and other attributes necessary for use in bioprocessing.

“A new part of the standard identifies metals commonly used in hygienic service and sets testing standards, properties, and other attributes for use in bioprocessing.”
mon austenitic stainless steels, 6 percent molybdenum super-austenitic stainless steels, and nickel-based alloys.

The new edition also has a new Nonmandatory Appendix I on vendor documentation requirements for new instruments.

**ADDITIONS AND CHANGES**

Several sections of Part SF Stainless Steel and Higher Alloy Product Contact Surface Finishes have been revised and augmented to reflect the addition of three new nonmandatory appendices.

Section SF-7 Electropolishing Procedure Qualification was revised to reference the new Nonmandatory Appendix H, Electropolishing Procedure Qualification.

Section SF-8 Passivation was substantially revised and augmented to include reference to the new Nonmandatory Appendix E Passivation Procedure Qualification.

Table SF-4 Acceptance Criteria for Passivated Product Contact Finishes was added to reinforce statements made in this section.

Section SF-9 Normative References was added, and includes references to important national and international standards regarding terms, definitions, and parameters for the determination of surface texture by profiling methods.

Section SF-10 Rouge and Stainless Steel was added. This section includes information on factors that may affect the formation of rouge, a term used to describe a variety of discolorations in high purity stainless steel biopharmaceutical systems. Rouge is composed of metallic oxides and/or hydroxides.

The presence of rouge in a system needs to be evaluated against its potential to affect the product, process, or long-term operation of the system. The new Nonmandatory Appendix D Rouge and Stainless Steel provides the methods to measure rouge in a system in both the process solution and on the actual product contact surfaces, and suggests various fabrication and operation practices to minimize rouge formation, and methods or techniques for its remediation.

A new subsection generated by the members of the Polymer-Based Materials Subcommittee (responsible for Part PM) has been incorporated into Part SF. Subsection SF-P provides acceptance criteria for polymer product contact surfaces for process systems and clean utilities, materials inspection techniques, and information regarding applications and surface conditions.

Part GR General Requirements includes an expanded section defining the qualifications for the Inspector’s Delegate, including documented training and qualification programs.

Part SD Design for Cleanability and Sterility adds substantial new content on the design of equipment and process systems plus significant updates to existing sections. The 2009 edition includes several new sections with requirements for the design of bioreactors and fermentors, sterilizers and autoclaves, clean-in-place distribution systems, and process gas distribution systems. The entire CIP Systems and Design section (SD 4.15) has been revised to meet current industry standards and expand requirements for clean-in-place skid design, CIP flow rates, cleaning process vessels, CIP supply and return headers, and CIP spray devices.

Part SD has also been updated with enhanced content on the design of hygienic pumps, ball valves, O-ring connections, top-entering mixers, and steaming for bioburden control.

Part DT Dimensions and Tolerances for Stainless Steel Automatic Welding and Hygienic Clamp Tube Fittings and Process Components has a number of changes and additions. They include creation of a new hygienic clamp face connection eliminating dead space and allowing for better cleanability, and a new table depicting hygienic ferrule face dimensions and tolerances.

The DT Subcommittee has several important projects going forward for future ASME BPE editions. They include collaboration with the Seals Subcommittee to develop a higher precision hygienic clamp with controlled intrusion, and collaboration with the Materials Joining Subcommittee to improve tolerances at orbital weld ends with the goal of improving weld repeatability.

Part MJ Material Joining has added a new paragraph, MJ-8.4, requiring that the weld metal and heat-affected zones of procedure qualification test coupons in duplex stainless steels meet the requirements of ASTM A923 Method A and/or C. The purpose of these tests is to detect detrimental inter-metallic phases in the weld.

Paragraphs MJ-9.2 and 9.3 have been amplified. Once a welding operator has been qualified to Section IX of the ASME Boiler and Pressure Vessel Code, he is allowed to perform welding outside the range of variables presented in MJ-9 (a) through (k) after performing a new test coupon which has been visually inspected and documented as meeting the requirements of Table MJ-3. The Material Joining Subcommittee added these rules to require the welding operator to demonstrate mastery of the operation of his machine.

The Material Joining Subcommittee is also working with the ASME B31.3 Process Piping Code Committee, which is in the process of adding a chapter on high-purity piping.

The BPE committee is seeking to increase international participation. There is a program in which members of an overseas group can send a delegate to meetings.

“...”
Part SG Equipment Seals establishes requirements for various mechanical seals and gaskets used with bioprocess equipment such as pumps, valves, rotating and reciprocating machinery, pressure vessels, and piping. For 2009 Part SG has added two new sections, SG-4.2 to cover O-rings fabricated from molded or extruded section using vulcanized molded joints and SG-4.3 to cover the application of seals for centrifugal compendial water pumps. Two appendices have also been added, one for standard process test conditions and the other providing a suggested application data sheet.

The BPE is still growing and evolving at a rapid rate. The subcommittee work is done by volunteers and much of the work is now accomplished between meetings by using improved communications technology such as e-mail and teleconferences. Drafts of new or modified parts are posted on a restricted part of the ASME Web site called C&S Connect that is accessible to committee members.

Meetings are open to the public and new members are welcome. There are three meetings a year, one in Puerto Rico, one in Europe, and one in the continental United States.

The committee is actively seeking to increase international participation. There are Asian and European voting members presently on the various subcommittees, and there is an ASME Delegate Program in which members of an overseas group can send a delegate to the meetings. To become a subcommittee member a candidate must attend three meetings, provide a letter of support from his or her employer, and complete the required paperwork.

The BPE, which was first published in 1997 and was revised in 2002 and 2005, has been on a two-year revision schedule for the past two editions, 2007 and 2009.

The next BPE edition is planned for 2012 rather than 2011. The three-year break will allow for the development of concepts with more additions and changes.

New for the 2012 Edition will be the addition of Part PI Process Instrumentation. This part will focus on requirements applicable to the design, installation, and use of instrumentation used in the bioprocess and pharmaceutical industries. Part PI will include instrumentation-specific attributes such as process performance and instrumentation serviceability that are not covered in other parts of the standard. It will address any process instrumentation and associated integrally mounted components in direct contact with the product, raw materials, or product intermediates.

Part PI is intended to provide minimum requirements for hygienic and process performance in coordination with the Process Analytical Technology initiative, a U.S. Food and Drug Administration program to assure quality without impeding innovation.

For additional information on the ASME Bioprocessing Equipment (BPE) Standard see http://www.asme.org/Communities/Technical/BPE.