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# Standardizing Equipment Design in the Biopharmaceutical Industry

**H**ave you ever wondered who started the first queue? And why? Was it a group that realized a queue brought order to their lives? Or was it during a dinosaur roast that one person said, "enough of this, form a line behind me!" I would guess that before that they recognized the need to standardize the methods of communications. Facial and body expressions were probably first since they are natural and take no formal training to learn. It didn't take formal training to recognize the speed at which a person was approaching, and the expression of sheer fright on their face, not to mention a reluctant guest of honor at that night's roast bearing down on them, that you also should consider changing from static to dynamic motion.

It was not by choice, but necessity, that formalized communication was developed. Drawings relayed stories and became official records. Then there was speech. Speech was good, but had its limitations. You could not converse with anyone outside of your tribe. The art of throwing stones at neighboring tribes to get attention sometimes met with disastrous results as it was misconstrued as a challenge and not as an invitation to dinner. Then someone said, "hold it!" This was probably the same person that said, "form a line behind me." This is ridiculous. There's got to be a more amiable and safer way to communicate with others outside of this tribe. We need to develop a standardized method or methods of communications. And so the ASME Council on Codes and Standards was founded. Actually, it wasn't for some years later that the council was founded, but time and space limitations forbid me the luxury of discussing all that transpired between the aforementioned period and the time the council was founded. In any case, at the time the council was founded, conditions were a bit more civilized. Speaking and writing were very popular by this time. It was now mechanical engineers who needed to standardize their communication efforts.

It was the industrial revolution and things were happening. The mother of invention, necessity, was very active. Machine tools, steam engines, and other forms of machinery to produce more goods and "make life and work easier" were in their formidable years. This meant more machines, more tools, and more inconsistencies.

All of these tools and machines applied basic design concepts. But new product design consistency for nuts, bolts, screws, parts, components, etc. did not exist. This prompted the outcry for standardization. In 1880, the American Society of Mechanical Engineers (ASME) was founded. It was no surprise that the first topics for discussion included the need to standardize the tools, equipment, machinery and terms and definitions associated with mechanical engineering.

Then in 1884, ASME developed and issued its first standard, a test code for boilers. Pipe and pipe threads were next to be targeted for standardization by ASME. The ensuing months and years saw further developments in standards.

In 1885, the society formed a committee to investigate the manner in which others around the world conducted tests of strength of materials. The committee's findings would be compared with the methods used in the U.S. This was the beginning of ASME's involvement with international standards development.

The need for uniformity in standards and ensuring consistency in fabrication and installation philosophies and techniques extends to the biopharmaceutical industry as well.

In the early days of pharmaceutical equipment manufacturing, specifications were loose, vague, and questionable. The 3A dairy standards were the basis for nearly all specifications written for equipment fabrication. These standards guided both the

specifier and the equipment manufacturer in designing and producing a piece of equipment that could:

- a) *Make product;*
- b) *Be totally self-draining;*
- c) *Be cleaned.*

However, the increasing need to be more specific and more disciplined meant following tighter specifications with more stringent requirements, such as those for surface finishes, which led to the introduction of the Root Mean Square (RMS) requirement. Slowly but surely, the original No.4 finish specification became a "No. 4 finish but with an RMS value." Thus, a specification would read "polish to a No. 4 with an RMS of 25-30."

Not all manufacturers followed the new standards requirements and the message they conveyed. The RMS values were overlooked. Owner representatives with the task of verifying the finish were equipped with "surface indicators" (profilometers). However, a number of manufacturers had never seen these machines. Up until this time, a No. 4 finish was achieved by a time tested standard way of grinding, buffing, and polishing. A comparator was used to verify the final finish. This was accomplished by holding a pre-finished, sample piece of the same material next to the production part. This method of verification was at times questionable and a matter of opinion. Furthermore, a pre-polished sample of a No. 4 finish from steel mill 'A' would not be the same as samples produced by steel mills 'B', 'C', and 'D'. Unless the sample was produced by the manufacturer of the equipment, or by the same steel mill that supplied the manufacturer, comparison of sample to end product was fruitless.

It was starting! Vendors (manufacturers) knew in order to stay in the game they had to purchase this equipment. Up to now, the requirement for a No. 4 finish was basic and polishing machines produced this finish using a specific grit paper or wheel.

Industry was starting to ask manufacturers to go a little further. There was now a value added to this standard No. 4. What was next? More stringent requirements for hardware and components, (i.e., hinges, nameplate brackets, castors for portable vessels, valves, etc.) and welding processes and techniques were also targeted and scrutinized. But most of all, it was design. In 1978 the US Government Food & Drug Administration (FDA) formalized the requirements known as Good Manufacturing Practices (GMPs). The Code of Federal Regulation (CFR) specifically required pharmaceutical companies to control all aspects of the manufacturing operations (as well as aspects of marketing, etc.). The CFR specifically addressed equipment used in the manufacture of drug products in Sections 211.63 - 211.72. These sections provided minimum requirements for the design, size, location, construction, cleaning, and maintenance of all equipment used in the manufacture, packing, or holding of a dry product. The interpretation and application of this standard was to evolve as the industry and FDA worked to gain greater definition of these terms. These industry practices and guidance documents were to improve harmonization of quality in the industry.

But still, inconsistency was rampant. For instance, a product manufacturing facility may have as part of its process a clean steam generator designed and built to ASME Section VIII, with an elec-

tro polished finish (E.P.) of 15-20 Ra. This would be piped to other equipment in another plant location. The tubing would be specified to ASTM A-270 supplement requirements S2 and electro polished to 15 Ra. Tube welding would be produced by the orbital welding process.

The receiving piece of equipment however would be "piped" with tubing that was hand welded with slightly less than adequate adherence to fit up, cleaning, handling, etc.

The industry was in need. The old adage in marketing "Find a need and fill it" was a true request if ever a request was made. But in this instance, it was not a marketing term for some up and coming corporation. It was an industry who recognized the need. Something had to be done. User and engineer specifications were scattered. What finish do we need? Should we electro polish? Do I need to passivate if I've already EPd? What pressure rated clamp do I use? The questions continued.

By 1988 the industry was ready for standardization. That same year, equipment manufacturers, material producers, end users, and engineering and construction organizations, all representing the biopharmaceutical industry, met at ASME headquarters in New York City to discuss what should be done. It didn't take long to agree that a need for consistency in design philosophies and techniques did indeed exist and that standards needed to be developed to accomplish this.

Then on June 20, 1989, the ASME Council on Codes and Standards issued a directive to the ASME Board on Pressure Technology Codes and Standards (BPTCS) to go forward with assembling an ad-hoc committee to address the industry's concerns and inconsistencies. This ad-hoc group was charged to review existing requirements and to recommend to the BPTCS whether or not a standing committee should be formed to pursue the development of requirements outlined above. After the initial meeting of the ad-hoc group, it was unanimously ascertained that there was a need to create a standing committee to develop a proposed standard. At the meeting of the BPTCS held during ASME's Summer Annual Meeting (SAM) in 1990, the ad-hoc group's report was presented along with the request to establish a standard committee to develop a bioprocessing equipment standard. This request was approved by the BPTCS at that time and we were "on our way."

The following scope was developed by the committee and approved by the BPTCS:

*"This standard is intended for design, materials, construction, inspection, and testing of vessels, piping, and related accessories such as pumps, valves, and fittings for use in the biopharmaceutical industry. The rules provide for the adoption of other ASME and related national standards, and when referenced, become part of this standard."*

And so, the ASME Bioprocessing Equipment (BPE) Main Committee was formed. This committee is made up of the following six subcommittees:

- General requirements (SC GR)
- Design for sterility and cleaning (SC SD)
- Dimensions and tolerances for stainless steel automatic welding and hygienic clamp tube fittings (SC DT)
- Material joining (SC MJ)

- Stainless steel and higher alloy interior surface finishes (SC SF)
- Equipment seals (SCSG)

*Note: It is to be noted that per ASME criteria, main committee membership must comprise a cross section of category of interest, not greater than 1/3rd total main committee membership.*

End users, manufacturers of equipment, and steel producers were solicited for comments regarding material, equipment, and system design concerns. The information gathered from these surveys allowed each subcommittee to focus on specific needs, not just on the general need of the industry requiring a standard.

The subcommittees were beginning to take shape. Survey results were reviewed and decisions were made as to which subcommittee would address or be responsible for addressing these concerns. This was not an easy task as some topics would cross over from one committee to another. For instance, some time into the standard's development process the subject of internal weld profile was discussed. The Subcommittee on Materials Joining developed its criteria for concavity and convexity. They even went as far as to employ an independent lab and an end user to help in determining hold up volume of tubes with predetermined finishes (mechanical and electro polished) and premeasured misalignments. The tubes were grouped in as-welded and non-welded conditions.

The Subcommittee on Surface Finishes claimed internal weld profile belonged in their part only because it fit their scope. They claimed the weld was part of the surface and this surface comes in contact with the product. It did not stop there. The design group was asked to review the hold-up volume results primarily for the weld misalignment information. How much mismatch can a system tolerate before turbulence becomes an issue? At what misalignment does cleaning become a problem?

During the standard's development, the committee kept close contact with ASTM, 3A dairy standards and the European CEN. This greatly reduced the risk of duplication between the four organizations. BPE liaisons to these organizations were asked to update the main committee at each meeting.

The committee kept focused on its goals and objectives. They were to develop a bioprocessing equipment standard that addressed:

- Consistency in equipment design as it related to cleanability and sterility.
- Standardize surface finish parameters and sealing methods, parts, and components.
- Determine the best practices for welding.
- Create industry standard terms and definitions.
- Standardize dimensions and tolerances for stainless steel automatic welding and hygienic clamp tube fittings.

In October of 1991, the call for help went out. ASME developed a flyer titled "Help Set Standards for Bio Processing Equipment" which was mailed to numerous organizations involved in the bioprocessing industry. The committee was "soliciting participation of all interested parties involved in bioprocessing". Meetings were scheduled and announced in Mechanical Engineering Magazine and all meetings were and still are open to the public.

Soon requests for committee membership began pouring in. Membership on the various subcommittees increased from meeting to meeting. A large number of members found it difficult to

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decide which of the six subcommittee meetings to attend. It was difficult for them to decide which committee would hold their interest the most.

During this time, it was not uncommon to enter a subcommittee meeting and find standing room only.

After five years of meetings and working on various drafts, in 1996 a final draft of the proposed standard was developed and approved by the BPE Main Committee. Following the main committee approval, it was sent out for public review and to the ASME Board on Pressure Technology Codes and Standards (BPTCS) for letter balloting. As a result of the comments received from the public review and the BPTCS letter balloting, the standard was revised once again.

Finally, the ASME BPE standard was approved for publication by the BPTCS and issued on October 17, 1997. The wait was over. Specification writing, reading, and interpreting is now made easier for end users, engineering firms, manufacturers, and material suppliers within the bioprocessing industry.

### *The ASME BPE Standard is organized as follows:*

As a brief overview of the standard, the general requirements part (GR) provides readers with an introduction, scope, and terms and definitions section. The general requirements subcommittee was responsible for coordinating the drafts produced by the other subcommittees, performing editorial reviews of each of the standard's six parts, and confirming the consistency of terms and definitions.

The design part (SD) focuses on industry requirements for cleanliness, sterility, and aseptic processing of closed bioprocessing systems and equipment. This part also delineates the methods, materials of construction, parts and components used to fabricate, operate, and sterilize bioprocessing equipment, parts, components, and systems.

The dimensions and tolerances part (DT) establishes overall dimensions and tolerances through graphic sketches and charts for sanitary tubes and fittings. It provides basic information for determining pressure ratings for tubing, fittings, and hygienic unions and delineates the method and format for their marking.

Soft metric equivalents are also given for dimension and tolerance values. These conversions from English to metric units are provided for reference only. They are meant as a guide for those unfamiliar with English units and require a recognizable metric equivalent.

The materials joining part (MJ) establishes the requirements for the joining (welding) of bioprocessing equipment including pressure vessels and tanks, piping, tubing, and fittings. It also addresses joining of non-metals and methods for the various allowable welding processes. Weld acceptance criteria (fit-up, concavity, weld geometry, etc.), non-destructive examination (NDE) methods (liquid penetrant, borescope, radiography, etc.) are also discussed. Weld procedures and performance qualifications are performed in accordance with ASME Section IX.

The stainless steel and higher alloy interior surface finish part (SF) provides criteria of interior surface finishes for bioprocessing equipment and distribution system components. It addresses

materials and the types of finishes (i.e., mill, bright annealed, mechanical polish, electro polish, etc.) and the methods used to achieve these finishes. This part also provides the criteria for identification and classification of typical surface anomalies (i.e., scratches, crevices, corrosion, porosity, oxidation, etc.). In addition, methods for cleaning, passivating, and sterilizing are also defined.

The equipment seals part (SG) defines the design and materials of construction of seals in bioprocessing equipment. This part also provides user basic design requirements, seal classes, materials of construction, and the various pump seals, valve seals, and seat designs that withstand product, sterilization, pressure, and temperature and meet FDA compliance while eliminating product contamination and release of potentially dangerous products to the atmosphere.

Part GR of the standard references 26 existing related codes, standards, and guidelines. It was not the intention of the committee to "reinvent the wheel." The primary reason for the close liaison with the European CEN, 3A dairy, and ASTM standards committees was (as stated earlier) to reduce the risk of duplication in standards writing. For instance, design, testing, and inspection requirements are presented in each part of the standard. The reader is referred to an existing code or standard and/or guideline specific to the particular paragraph being read. As an example, Paragraph MJ-7.2.2 Piping, instructs the reader to perform visual examinations "in accordance with the provisions of ASME B31.3, Section 344." Personnel performing examinations of piping systems shall meet the requirements of ASME B31.3, Paragraph 342.1...."

Some may ask, with all this talk and all these meetings, the time devoted by all these men and women, what was their vision? What did they expect to get for all their trouble, time, and expenses? Some were just curious; others were looking for self or company notoriety, while a dedicated group had a sincere desire to help to end the frustrations and inconsistencies plaguing the industry. There were also those who had a stake in any design decisions that would be made.

As if in some sort of racing competition, a few manufacturers jumped the gun on quoting verse or copying tables from the BPE standard years before the BPE Main Committee and ASME BPTCS/ANSI approval. It was as if this new standard was a hot news story. Everyone wanted to be the first to release it. BPE Main Committee members would get calls from contractors and end users stating they had received proposal documents with excerpts from the standard. They would ask, "When was the standard published? Where and how can we get a copy?"

It was difficult keeping the developing standard under wraps. At the beginning of each of the BPE Main Committee meetings an announcement was made that the standard as it stood was for "our eyes only." But just like the White House, we had leaks and they were difficult to stop.

The standard was published in October 1997 and received great reviews. But the work is not over yet. This is a living document. The ASME BPE main and subcommittees still meet twice a year to review, expand, and modify the standard. During the past two meetings, the subcommittees met to discuss modifications and

additions to their specific parts. The results of these meetings will become the standard's first addendum that is due out this fall.

In July of this year, both the ASME BPE Main Committee and ASME BPTCS were issued letter ballots of the proposed ASME BPE Standard addenda and are expected to vote on the changes/modifications made to the various parts of the standard. Once approved, subscribers to the standard will receive a copy of the addenda.

The number of subscribers to the BPE Standard is increasing as people are becoming aware of its existence. More and more equipment and material producers are embracing its concepts. Engineering firms and end users are adopting it and making reference to the standard in contractual documents.

The ASME BPE Standard benefits both the end user and the manufacturers by providing consistency and uniformity in written and verbal communications. Yes, there will be a certain indecisiveness as to what finish is really needed or the level of inspection required, but the standard lessens the need for lengthy performance

specifications. I'm not suggesting a specification writer should limit his/her specification to a single statement such as "design, build, install in accordance with ASME BPE Standard 1997." What I am suggesting is that there will be a better understanding of what is really required by both parties. Product, equipment, and material manufacturers will find it will take less time to quote schedules and costs predicated on specification requirements since customer requests (specifications) will reference the BPE Standard.

The industry will realize a substantial savings in both time and money since the effort in writing and interpreting specifications will be reduced to a minimum.

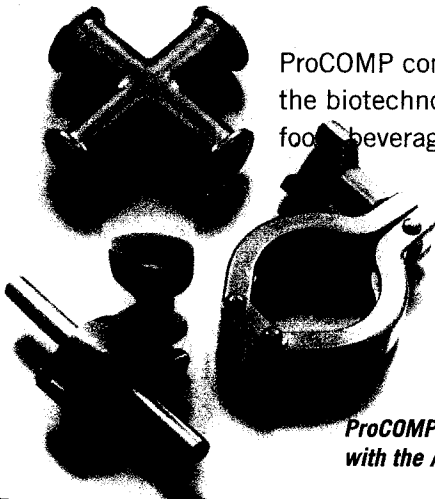
This brings us to the benefit of using manufacturers who subscribe to and have adopted the BPE Standard. I could easily say it's beneficial to use manufacturers who subscribe to the BPE Standard because you know what you are getting. By adopting this standard, the manufacturers are making a statement that they are part of the change to uniformity ■

*Mr. Cirillo serves as Vice Chairman of ASME's Bioprocessing Equipment (BPE) Main Committee and as a member of ASME's Board on Pressure Technology Codes and Standards. He has over 25 years of broad-based experience in quality control and quality assurance for the pharmaceutical, biotechnology, food and process industries. He is currently Manager of Quality Assurance for Life Services International, a division of Day & Zimmerman International Inc. In this role, he is responsible for managing and directing inspection personnel in addition the administrative and technical overview of QAIQC activities. He also provides field liaison support at project construction sites for all tasks relating to the field installations of mechanical equipment and hygienic tubing/piping systems.*

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