

Designing a CGMP Bioprocess Equipment Manufacturing Facility

Fabricating Bioreactors and Fermentors to the ASME Bioprocessing Equipment (BPE) Standard

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A GMP facility is, by definition, a facility designed, constructed and operated in accordance with current good manufacturing practices (CGMP) guidelines established by the FDA. By inference, a manufacturing facility that produces CGMP equipment must also meet criteria with respect to SOPs, documentation, and utilities that are involved with product-contact surfaces. Here we describe how one manufacturer has designed and organized its facility and established working procedures for production of GMP bioprocessing equipment. Procedures were developed for orbital welding and documentation for compliance with the most recent ASME Bioprocessing Equipment Standard (BPE 2005) (1).

Planning, preparation, and construction of a new facility gave Sartorius BBI Systems, Inc. (SBBIS, a subsidiary of the Sartorius Group of



Photo 1: Fermentor with associated control system nearing completion on the manufacturing floor

Germany) the opportunity to design and organize this facility to improve workflow and efficiency and to streamline procedures. The facility replaces five separate buildings and is “Y”-shaped like an antibody. It has a primary assembly and test floor, feeder shops organized to optimize work flow, and offices housing sales, engineering, production, and QC, all under one roof.

Several offices are provided for FAT (factory acceptance test) and third-party QC personnel. A document prep room allows an organized methodology for preparation of turnover package (TOP) manuals. An ample supply of conference rooms is helpful if several clients are in-house at the same time. The new Pennsylvania facility is a hub for Sartorius North America now that SBBIS is more integrated with the Sartorius Group Biotechnology Division. A special video conference room brings people together from sites and other Sartorius locations for electronic face-to-face meetings. The engineering department takes full advantage of this excellent communication

tool when dealing with customers during the design phase of custom-engineered projects. Their goal is to perform engineering 24 hours a day by using the engineering capabilities of facilities in Pennsylvania, Germany, and India.

Supporting final assembly and FAT steps is an array of pure-water, clean-steam, and clean oil-free air utilities. These utilities are distributed throughout the shop to assure that product contact surfaces, once welded and electropolished, never come into contact with potable city water, plant steam, or dirty air. Products manufactured by SBBIS range from fermentors (Photo 1) and bioreactors up to 30,000-L working volume (2), integrated CIP carts, filtration systems, waste inactivation systems, and membrane- and ultrafiltration (MF–UF) crossflow purification skids for CGMP facilities. In conjunction with the equipment built, services offered include electropolishing (EP), NIST-traceable calibration, massflow meter calibration and repair, equipment repairs, and maintenance contracts.

For joining of tubing and components, SBBIS uses automatic orbital welding to meet the ASME Bioprocessing Equipment (BPE) Standard (1). Finished assemblies are electropolished on site instead of at a separate facility.

ASME BPE STANDARD

The ASME BPE standard was introduced in 1997 as an American national standard for bioprocessing equipment. A second edition followed in 2002. By that time the

PRODUCT FOCUS: ALL BIOLOGICALS

PROCESS FOCUS: BIOPROCESS FACILITY AND EQUIPMENT DESIGN

WHO SHOULD READ: PLANT AND PROJECT MANAGERS, PROCESS AND EQUIPMENT DESIGN ENGINEERS, MECHANICAL CONTRACTORS, QA/QC PERSONNEL

KEYWORDS: BIOREACTORS, FERMENTORS, CGMPs, ASME BPE, ORBITAL WELDING, PASSIVATION, ELECTROPOLISHING

LEVEL: INTRODUCTION

BPE had become an international standard adopted by 29 countries. Although originally intended to be applied solely to bioprocessing equipment, the scope has extended to include the pharmaceutical and personal-care industries. The original concept was to provide guidelines for design and construction of bioprocessing equipment, including components, assemblies, and systems, in a way that would optimize cleanability and sterilizability. The BPE standard provides manufacturers, end users, and engineers with a single language and a common understanding by enabling them to share in the numerous design and installation methods and philosophies used in the industry.

Improving communication by exchanging information that would previously have been kept proprietary has facilitated consistency and uniformity in the biopharmaceutical industry. This enhances productivity and helps maintain the integrity of biopharmaceutical products. Product uniformity and integrity are essential not only for the US biopharmaceutical community, but also for the broader international community.

Within the BPE, various subcommittees define standards for bioprocessing equipment including designing equipment for sterilizability and cleanability, establishing surface-finish requirements for stainless steel, controlling the dimensional tolerances of fittings, joining of components by orbital welding (3), and for evaluating acceptance criteria for welds and for metallic materials used in bioprocess equipment, and other related topics. The standard applies only to components that are in direct contact with products, raw materials, and product intermediates during manufacturing, development, or scale-up.

MANUFACTURER'S QUALITY ASSURANCE PROGRAM

One of the fundamental guiding principles of the BPE Standard is the requirement for a manufacturer's quality assurance program. The General Requirements Part GR-7 of the 2005 Edition states that "the manufacturer shall implement a quality assurance program describing the systems, methods, and procedures used to control materials, drawings, specifications, fabrication, assembly techniques, and examination/inspection used in the manufacture of bioprocessing equipment"

(1). Therefore, SBBIS has designed such a program and has designed and arranged the facility to most efficiently fabricate equipment with the necessary controls and documentation as listed in the "Facility Arrangement" box.

BIOREACTORS AND FERMENTORS

The vast assortment of customized skid designs produced in this facility requires consistent SOPs to assure use of proven production methods and that quality is built-in as designed. Such systems are typically highly automated and controlled by proprietary systems in combination with PLC and DCS based commercial systems. In addition to stringent production methods, SOP testing provides a stringent guide for assuring complete functionality in accordance with GAMP (good automated manufacturing practices) requirements (specifications for functional requirements and software design).

Successful FAT test protocols show that each GMP design meets the BPE standard. These protocols are commonly used as part of a customer's IQ/OQ documentation. In fact, ICV (integrated commissioning and validation) has become a standard practice by which SBBIS shortens the timeline for clients through installation and validation cycles.

A complete TOP is paramount to successful ICV completion (4). It requires all critical product components to be fully traceable regarding material certificates and joining methods used for assembling SS tubes and SS components. Consider a TOP as a traceable document trail from production of component-wrought parts at the mill through final assembly in bioprocess equipment and finally into the drug production arena where injectable product eventually finds its way into patients. Full traceability requires this type of thinking, and SBBIS requires this same type of thinking of all its critical component suppliers.

ORBITAL WELDING

BPE "Part MJ-4.4 Tubing" states that "welding on tubing shall be done using automatic (or machine) welding techniques (such as orbital tube welding or lathe welding), except where size or space will not permit." Nearly all the tubing welds on product contact surfaces for biopharmaceutical applications are

done with autogenous (without the addition of filler) orbital gas tungsten arc welding (GTAW). The joint design for hygienic tubing and fittings is a groove weld in square butt configuration, otherwise known as a square butt joint, which requires the ends of tubing and components to be machined square so they fit together without gaps.

For orbital tube welding, a nonconsumable tungsten electrode is installed in the rotor of an enclosed weld head. (*Consumable* in this case means that the electrode does not melt into the weld, although it does need to be replaced after a certain number of welds.) The weld head is filled with inert gas that protects the electrode and weld pool from oxidation. An arc is struck between the electrode and the work, and the electrode rotates around the joint to complete the weld. Because the weld head and the tubing remain in-place, this is an all-position weld with the electrode moving both uphill and downhill during the course of a weld. When a weld moves downhill, there is a tendency for the liquid metal to flow into the electrode, which could potentially short out the arc. Therefore, pulsing the weld current between a higher and a lower current pulse alternately melts and cools the metal, providing control of that weld pool or "puddle."

Orbital welding has been accepted as an industry standard not only because an orbital weld bead's smooth surface facilitates cleanability, but also because welds of the same high quality can be achieved consistently, weld-after-weld, whether in the field (where 30,000 welds for a new facility are not uncommon) or for high-productivity welding in a shop environment.

The BPE weld criteria (2, 3) of full penetration, smooth inside- and outside-diameter (ID and OD) surfaces without excessive concavity or convexity, good alignment of parts, and lack of discoloration (4) are all part of the BPE design concept for limiting the growth of microorganisms by facilitating cleanability and sterilizability. A rough or pitted surface, an unpenetrated or discolored weld would form crevices for contamination that would make cleaning problematic. In fact, the functionality of modern CIP systems relies on a smooth ID surface and would not be nearly as effective without orbital welding technology.



Photo 2: Five of the six Arc Machines orbital welding power supplies equipped with water cooling units in the welding room; note documents at each weld station that travel with the weld assemblies.



Photo 3: A welding operator initiates an orbital weld. A pipe stand is used to support the tubing assembly. The built-in purge system shown above the power supply delivers high-purity argon gas for purging the weld in the enclosed type weld head and to the tubing ID.

Sartorius BBI Systems is well-experienced with orbital welding, having owned equipment since 1992. The new facility has six Model 207 orbital welding power supplies and several sizes of weld heads from Arc Machines, Inc. (Pacoima, CA, www.arcmachines.com). Each weld head accommodates a range of sizes by changing inserts that accommodate each tubing diameter. The head is mounted on the bench by a bench-mount bracket that lends stability to the weld set-up (Photo 3). Welding generates heat, and if heat is allowed to build up, it can cause the moving parts of the weld head to expand and move less freely. Overheated cables wear quickly. Water cooling units placed beneath the power supplies circulate water through the cables and weld head to keep the equipment running smoothly.

PURGING

Purging both the inside and outside of a weld joint with inert gas during welding is one of the most critical factors for achieving a hygienic or high-purity weld. Ideally, the base metal should not change



Photo 5: Gas supplies and controllers outside the weld lab; pure argon is used for orbital welding whereas for manual welding, argon from a cryogenic dewar is mixed with hydrogen (2%) from a gas cylinder using a mass flow controller. Gas is piped to each weld station for purging during welding.

FACILITY ARRANGEMENT

The Sartorius BBI Systems facility implements a quality assurance program in accordance with the ASPE BPE standard. Design elements include

- Offices and engineering in one area to foster rapid communication
- Large, open main production area where tanks and vessels are assembled onto skids with associated welded tubing assemblies and automation controls
- Distribution of clean utilities in stainless steel distribution piping (all material and welds validatable)
- Large area for quarantine of incoming materials and materials examination
- Segregated storage areas for project materials
- Isolated, clean, temperature-controlled orbital welding production room (Photo 2)
- Machine shop
- Electrical assembly shop
- Frame shop for welding frames for equipment skids using the gas tungsten arc welding (GTAW) process. This method avoids grinding, which would create potential contamination. Frames are polished as necessary to meet various customer requirements.
- Electropolishing laboratory

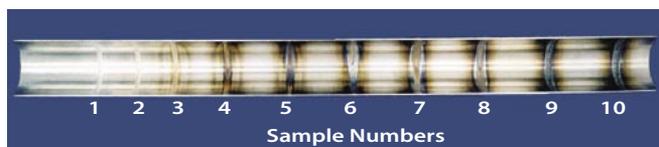


Photo 4: Figure 1 from the AWS D18.2 standard shows discoloration on the ID of a 316 L stainless steel tube. Discoloration is proportional to the amount of oxygen in the ID purge. Sample 1 had 10 ppm O₂, and Sample 10 had 25,000 ppm.

color, but that may be difficult to achieve. For biopharmaceutical applications some color change is permitted on the non-product-contact surface of the weld, but none is permitted on the weld, and only a slight amount of change is permitted in the heat-affected zone (HAZ) of the product-contact surface. For biopharmaceutical applications this typically means a color change no greater than that of sample number 3 of Figure 1 in AWS D18.2 (www.aws.org), and preferably even less (Photo 4).

It is well documented that weld discoloration, or *heat tint*, as it is sometimes called, reduces the corrosion resistance of stainless steel in proportion to the amount of color. Because gas impurity levels, particularly contamination with oxygen and moisture, have a detrimental effect on weld discoloration, it is important not

only to specify gas of a particular purity level, but also to maintain that level at the weld joint throughout the weld process. All orbital welding at the SBBIS facility is done using 100% argon with a 99.96% purity certificate.

SBBIS has built a purge system with a satellite telemetry refillable argon storage tank. The liquid argon tank is followed by an ambient vaporizer and stainless steel distribution piping throughout the orbital weld shop. This allows use of shorter polyethylene purge hoses that connect the weld head and the tube ID purge to the source, thus minimizing the time gas could be exposed to atmosphere diffused through the plastic.

Precise control of the purge gas flow rates is critical, both to the weld head and to the tubing ID. The flow rates are set by independent flow meters for each purge line. Excessive flow to the weld head (OD surface) can disturb the arc, whereas excessive flow to the ID can result in concavity or may even blow out the weld. A Magnehelic pressure gauge (Dwyer Instruments Inc., www.dwyer-inst.com) is sometimes used to determine the correct flow rate to the weld ID.

For sanitary manual welding, a high-purity argon dewar and hydrogen in cylinders are located just outside the weld shop (Photo 5). The high-purity gases are mixed to a constant percentage of 98% argon and 2% hydrogen using a mass flow controller and distributed by a stainless steel tubing system into the weld lab with a separate point-of-use connection for each manual welding station. Adding a small amount of hydrogen to the inert argon shielding gas makes the welding arc somewhat hotter for better penetration, but it also provides a reducing atmosphere that results in less discoloration than with straight argon if there is any amount of oxygen in the purge gas.

This facility can produce more than 100 high-purity welds each shift with a rejection rate of less than 2%.

TURNOVER PACKAGE DOCUMENTATION

The "Materials Joining Part (MJ-10)" of the 2005 BPE standard lists documents required for a TOP (2, 5) to be turned over to an owner for CGMP-validated distribution systems. Such systems include tubing systems on modules, super skids, and skids and the shop or field fabrication



Photo 6: A welded assembly with its control document (yellow) and weld map showing location of the assembly with each weld numbered on the CIP pump for a 750-L fermentor

of tubing. ASME BPE compliance requires that every weld on a product contact surface in a biopharmaceutical plant must be identified on a weld map (such as the isometric drawing shown in Photo 6). It must be fully traceable back to the original components, with heat number codes for each component, the date it was welded, the welder's identification number, and whether or not the weld was inspected (5).

The TOP must include material test reports (MTRs), certified material test reports (CMTRs), certificates of compliance (C of Cs), and material examination logs. Sartorius BBI uses an incoming material examination log similar to that included in the appendix section of BPE 2005. Material test reports for fittings and process components including tubing, valves, pumps, filter housings, and instrumentation must be verified to the applicable specification(s) and be marked with a heat number or code traceable to a material test report. Weld ends of fittings and other components to be welded must be faced with a square-cut end free from burrs, must conform to BPE dimensional tolerances, and must otherwise be ready for welding.

All incoming items at SBBIS are received, assigned an internal part number, and placed in the quality control receipt examination area. Once a part has been examined and accepted, it is ready to be used in a project. If for any reason it is unacceptable, a "hold" tag is placed on it, and it is placed in a quarantined area and may not be used. Each project or weld assembly has a work order, a drawing, and a bill of materials. A file is compiled for the project, and control documents accompany the work order throughout the various stages of

production and become part of the TOP.

This QC process helps to ensure that all material meets specification; for example, that a component of a less corrosion-resistant grade such as type 304 stainless steel, which lacks the molybdenum addition present in 316L, is not used when type 316L was specified. It is also important to verify that weld ends specified as meeting the BPE specification are marked "BPE" when received. Even if the item was 316L and conformed to the American Institute of Steel and Iron (AISI) specifications, it may not conform to the BPE chemistry for weld ends, which limits both the upper and lower concentrations of sulfur, or to the BPE requirements for surface finish. Sulfur has a profound effect on weldability. The limited range specified by BPE of 0.005 to 0.017 wt % is designed to eliminate difficulties of welding very low sulfur materials or those with larger differences in sulfur concentration that may be difficult to weld.

The BPE surface finish specification is also documented because a rougher-than-specified surface finish can hamper cleanability and reduce corrosion resistance. The control document is important to assure traceability from the mill to the component manufacturer and though welding and finishing at SBBIS. Thus the components of any finished weld assembly on a skid or in a system can be identified by ISO drawing number, internal part number and date of welding as well as the results of examination or inspection (Photo 6).

WELDING DOCUMENTATION

Welding documentation is also part of the TOP. This includes documents certifying welding procedures and welding personnel to ASME Section IX of the boiler and pressure vessel code, which consist of welding procedure specifications (WPSs), procedure qualification records (PQRs), and welder performance qualifications (WPQs) for manual welders, as well as welding operator performance qualifications (WOPQs) for orbital welding operators. The qualifications for inspectors and examiners must also be included.

Sartorius BBI Systems generates sample welds, also known as coupons, at the beginning of each day on the sizes being welded that day as part of its required QA/QC program. A sample weld log is

maintained for all projects. The production information includes the sample number, date, size, welder identification number, weld machine serial number, and weld program number. Examination information includes a QC signature, date of examination, whether the coupon is accepted or rejected (A/R), and any relevant comments.

Each welded coupon is placed in a clear plastic bag with the weld print-out from the welding power supply. Although weld sample logs are maintained indefinitely, the actual coupons are retained only for the life of a project.

The ASME BPE, in accordance with the ASME B31.3 process piping code, distinguishes between examination and inspection. B31.3 requires that the external surfaces of all welds be examined, and a minimum of 20% of the welds be inspected internally on the product contact surface with a borescope or, when accessible, by direct visual inspection. The installer or person performing a weld makes the examination, and the owner or its representative (which may be a third-party QC company or a consultant) performs the inspection. The contractor must submit an inspection plan in which the percentage of welds to be inspected must be agreed on by the owner and/or user, installing contractor and/or engineer. The requirements for personnel performing examinations and inspections are listed in ASME B31.3 Chapter VI, paragraphs 340.4, 342.1, and 342.2.

Passivation and Electropolishing:

Typically in biopharmaceutical facility-wide piping systems, welds are put into service in the as-welded condition. The only postweld treatment is passivation, which is a chemical treatment with nitric acid or citric acid with chelants to remove free iron (6). Although passivation helps restore the passive protective film on stainless steel that is disturbed by welding, it does not remove discoloration, which requires a more aggressive chemical treatment.

At SBBIS, welds on fittings or assemblies that are in product-contact piping systems are always electropolished after welding. Electropolishing is a controlled electrochemical process using an acid electrolyte, DC current, anode, and cathode to smooth the surface by removal of metal. It is actually a form of aggressive chemical passivation. Unlike weak chemical passivation,



Photo 7: A technician in the SBBIS electropolishing facility prepares a part for electropolishing. This “hands-on” process is still operator dependent.

electropolishing can actually remove discoloration produced by welding if a reasonable inert gas purge was present during welding. It can also improve the Cr:Fe ratio to restore corrosion resistance. Electropolishing removes the underlying layer of metal that has had some chromium depleted from the welding process. This helps restore the loss of corrosion resistance that occurs during welding and provides a smooth surface that facilitates cleaning and control of microorganisms when placed in service.

SBBIS has found it much more efficient and practical to have an electropolishing (EP) facility in house (Photo 7). When welded assemblies are completed, they are placed on a shelf in a bin, and those items requiring electropolishing are flagged and sent directly to EP without having to be shipped offsite and back again. The 2007 edition of the BPE standard will require that an electropolishing vendor have and use a quality control program for its EP system and that it qualifies its EP methods in accordance with a written procedure. Acceptable ranges of EP essential variables must be specified in the procedure. Such variables include, but are not limited to, amperage/time as defined in amp minutes per square inch (surface area \times amps provided \times minutes processed); and temperature range of bath during process (min–max temperature range). SBBIS has proprietary procedures, and all of this is documented to be prepared well ahead of a project.

UNIFORM, HIGH-QUALITY FABRICATION

When the developers of the BPE standard began to write it in the late 1980s, one topic they focused on was orbital welding technology, which offered a more

hygienic solution to facility piping design and installation practices. Orbital welding has now virtually replaced all manual welding for product contact surfaces in biopharmaceutical installations that use the standard. The conversion of the BPE standard from a national to an international standard makes uniform, high-quality fabrication technology feasible anywhere in the world.

Sartorius BBI Systems was an early leader in the new technology, having purchased its first orbital welding system in 1992, long before the first ASME Bioprocessing Equipment Standard (BPE-97) was introduced. The company continues to develop orbital welding practices and procedures in synchrony with or even in advance of changes to the BPE standard, advancing production procedures and documentation for fabrication of bioprocessing equipment for use in CGMP facilities worldwide.

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