

This two-part article is a case study tracking the installation of process piping for (product) filling lines 7 and 8 in Building 21 at the Sicor, Inc. (formerly Gensia Sicor Pharmaceuticals) plant in Irvine, California.

Part 1 includes planning, demolition of existing structures, and preparation for the new installation.

Installation of Pharmaceutical Process Piping - A Case Study

Part 1 - Planning and Preparation

by Barbara K. Henon, PhD, Stephan E. Muehlberger, and Gene DePierro

Introduction

Good process piping is fundamental to the success of any pharmaceutical or biopharmaceutical installation. All systems including process equipment and piping, must be fully drainable, cleanable, and sterilizable for the successful production of pharmaceuticals. Over the past decade, advances on several fronts have contributed to make the installation of process piping more efficient and with fewer delays.

As an example of current installation practices, this article is a case study of a process piping installation at a project for Product Filling Lines 7 and 8 in Building 21 at the Sicor Inc. Pharmaceutical Plant in Irvine, California from the summer of 2002 until its completion in March, 2003. In support of the product lines, piping systems for nitrogen, Clean-In-Place piping (CIP), Water For Injection (WFI), Reverse Osmosis (RO) water, Deionized (DI) water, product clean steam, and clean steam condensate were installed.

Projects such as this must be planned in advance by the owner and activities coordinated between the design engineer, general

contractor, installing contractor, third party QA (also referred to as the inspection contractor), and the validation team.

Before beginning construction, the owner must have a very clear idea of exactly what he wants the system to look like and how he wants it to function. Computer simulations help to visualize the project before the engineers and vendors are called. Mechanical contractors have greatly improved their fabrication technology for installing process piping. They now have better defined procedures and fewer "cut-outs" of welds which has meant "cleaner" documentation submitted for FDA approval. As a result, productivity is higher.

This is partly due to the widespread use of orbital welding and the development by the installing contractors of orbital welding Standard Operating Procedures (SOPs). These SOPs are written procedures followed by welding personnel so that everyone follows the same series of steps in the same order for handling materials, cutting and end-prepping of tubing for welding, inert gas purging, and welding, etc.

Improved standards and guidelines such as the ASME Bioprocessing Equipment Standard

Figures 1A and 1B. "Before" and "after" pictures show renderings of the desired "look" as a pre-construction Computer Graphic Image (CGI) on the left, while the actual appearance of nearly completed room is shown in the photo on the right. *CGI and photo courtesy of Sicor Inc.*



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(BPE-2002) originally published in 1997, and the ISPE Baseline® Guides^{1,2} also have driven the quest for quality in pharmaceutical piping systems. These standards were developed by industry leaders who recognized that good design and efficient installation procedures are important for containing costs both during construction and for the service life of the systems.

This installation would be considered a “small” process piping project with about 2,500 feet of stainless steel tubing with a total of approximately 600 orbital welds. This works out to be a weld every 4 to 5 feet. Sicor Inc. is nearly unique in the number of products they produce with more than 100 different drugs made at this facility. Their products include Active Pharmaceutical Ingredients (APIs) for use in various products, Finished Dosage Products (FDP) (injectables), and biopharmaceuticals such as human growth hormone and human insulin.

Defining User Space

Senior Project Manager for Sicor, Stephan Muehlberger, begins a project by defining the user space. He develops computer simulations of the proposed spaces using software which provides extremely accurate visualizations of how the completed rooms and suites will appear when finished. The end-user is most concerned with the appearance of those areas with the highest requirements for cleanliness. He has a certain “look” in mind for the high-visibility areas which include the filling suite, the area of compounding, and the component preparation area. Not coincidentally, these happen to be the areas with the highest ratio of process piping.

Once the location of equipment in these areas is established, engineers can concentrate on how to get the utilities to the spaces. Computer simulation is a very powerful tool that allows the viewer (engineer or contractor) to virtually open doors and walk through a series of proposed areas and to view the spaces from above to see how various pieces of equipment will be placed in a room. From this perspective, they are able to gauge the amount of walk-around space that should be available around each component. The work space must be uncrowded, clean, and orderly with everything in its proper place.

The filling lines project has 20 cleanrooms ranging from Class 100 up to Class 10,000. The number and location of sinks and use points must be detailed in advance. Arrangements must be made for HEPA filters, HVAC, temperature controls, and piping. To prevent crossing of piping and ducting or similar disorderly arrangements, the areas to be left clear must be specified. A computerized presentation can provide sufficient detail to serve as a guide for writing the job specification and help to keep change orders to a minimum.

If a particular computer drawing of a process panel shows the exact position of a valve with respect to the piping, this can help serve as a guide for the installing contractor - *Figures 1A and 1B*. On a similar project, computer simulations saved an estimated 10% of the project cost and helped the owner to get what they wanted.

General Contractor

The general contractor specializing in construction projects for the Biotech and Pharmaceutical Industry was the liaison between the architect engineering firm, the end user, and the construction team. Project Executive, Larry Moore, was responsible for overseeing the entire project. The general contractor prepared the master document for the installation called the *Construction Qualification Program (CQP)*. The CQP consisted of a set of written SOPs and guidelines for the purpose of controlling the construction process. The procedures covered documentation compiling, system and equipment testing, and the requirements for Turnover Package preparation.

Written procedures are considered to provide the best assurance that the important systems and components of a pharmaceutical manufacturing facility are installed in accordance with the specifications and that the proper installation has been documented giving a high level of assurance that the principles of current Good Manufacturing Practices (cGMP), as interpreted and enforced by the United States Food and Drug Administration (FDA), have been met.

The FDA does not tell people how to build a facility, but rather checks to see that all the documentation is correct. End users and their validation and QA people must demonstrate that they are in compliance with 21 CFR 211.65 paragraph (a) which states “*Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*”³ If any of the documentation submitted to the FDA is found to be out of order, the FDA will start “pulling at threads” to get at the root of the problem.

Installing Contractor

Project Manager Stephan Muehlberger said that in a perfect world he would be able to just tell the vendor to “install the process pipe” and it would be done not just to the standard, but exactly the way he wanted it. Since it is not a perfect world, he must have a relationship with the vendor and know their level of experience and expertise. The installing contractor, who has done previous work for Sicor and are an approved and preferred vendor, did design-assist and project

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Figure 2. Welding operator installs an electrode in the orbital weld head which is connected to an orbital welding power supply. A water cooling unit is situated beneath the power supply. *Photo courtesy of Pro-Tech Process, Inc.*

coordination and execution. Their welders are experienced in the use of orbital welding equipment - *Figure 2*. They understand what's required in terms of how the system should look, how to do the isometrics, and the best way of supporting the piping. Proper pipe support is important since the plant is in California and must conform to requirements for seismic zone 4.

IQD Turnover Package

In preparation for Phase I construction, the installing contractor prepared an IQD Turnover Package for each system that was to be relocated including process gases, clean steam, etc. The IQD Turnover Packages each contained a Scope of Work statement, a list of project personnel and their brazing certificate, or for welded systems, welder performance qualifications, Weld Procedure Specifications (WPS), and Procedure Qualification Records (PQR) in compliance with ASME Section IX of the Boiler and Pressure Vessel Code.⁴ Also included were welding equipment certifications, receiving logs for materials, critical system isometric (ISO) drawings for each of the systems, certificates of cleaned material, and pressure test reports for various system components.

Welded systems had coupon logs, weld logs, borescope logs, and passivation procedures and certificates. At the end of the IQD Turnover Package, there was a sign-off sheet to be turned over at the end of the shutdown for acceptance of the work by the client. The Scope of Work for the shutdown was to isolate and remove process gas lines from the first floor labs in the demolition area and tie-in and re-route process piping systems.

The installing contractor translated engineering drawings from the architect engineer from two-dimensional to three-dimensional isometric construction drawings and then verified that the drawings were "constructible." The general contractor obtained the necessary permits from the city to do the work.

Phase I, June 14 - July 30, 2002, Demolition and Re-Installation of Existing Systems

The first phase of the piping installation was a shut-down to accommodate a "Tenant Improvement" (TI) situation. This involves relocation of the existing equipment and utilities in the area where the new product lines were to be installed in order to avoid interruption of the then-current production schedule. The demolition phase was on a very tight schedule with crews working around the clock. Bulldozers were used for demolition of walls which were cut down and moved out in large chunks; utilities, lights, phones, fire alarms, etc. were all cut out and then equipment was relocated and re-installed. All process equipment, utilities, and piping had to fit within very confined spaces and there could be no interference among the plumbing, electrical, concrete, carpenters and other trades who had to work in the same space at the same time to complete this phase within the allotted time.

Phase II

In preparation for Phase II, the installing contractor prepared a separate submittal package for each of the piping systems which included the product lines and piping systems for nitrogen (N₂), Clean Air (CLA), Clean-In-place (CIP), Water For Injection (WFI), Reverse Osmosis (RO) water, Deionized (DI) water, product clean steam, and clean steam condensate. For example, the WFI submittal package contained a specification for stainless steel piping materials, such as tubing and fittings, and methods of attachment which included flanges and gaskets, orbital welding, and valves. The remainder of the book contained vendor product information and specifications for the above items as well as for piping insulation material and instrumentation. An orbital Weld Procedure Specification (WPS), qualifying the welding procedure to ASME Sect. IX of the Boiler and Pressure Vessel Code⁴ and Procedure Qualification Records (PQRs) for each of the welders and isometric drawings for routing the WFI system also were included in the package.

Typically, material availability drives the schedule which means that items with long lead times must be ordered as soon as possible. For this project, the long lead time items are one-of-a kind custom pieces of equipment such as WFI heat exchangers, valve clusters, and other process equipment.

Orbital Welding

During the past decade, the ratio of orbital welds to manual in biopharmaceutical systems has increased to the point that presently very few manual welds are done. Dr. Richard Campbell of Purity Systems, Inc. reported at a recent ASME BPE Standards meeting that about 99% of welds in biopharmaceutical installations are now done with orbital welding. The BPE standard requires that, if a manual weld is done, it must be with the owner's permission and it must be inspected on the inside (ID) with a borescope as shown in Figure 3.

The welding used in hygienic biopharmaceutical applications is autogenous orbital GTA welding. In this process, an

arc is struck between a non-consumable tungsten electrode and the weld joint. This takes place inside an enclosed weld head in an inert gas atmosphere. The tube or fitting being welded remains in place while the electrode in the weld head rotor moves around the joint circumference to complete the weld. Weld parameters such as welding current, electrode travel speed, and pulse times are programmed into the microprocessor-controlled power supplies (Figure 2) and stored as weld programs or weld schedules for each size of tubing, pipe, or component to be welded. Print-outs of weld schedules are included in the weld qualification documents. The weld joint configuration is a square butt preparation in which the tube ends are cut square and machine-faced to fit together without a gap.

The goal of orbital welding is to achieve a very high degree of repeatability from weld to weld, not only to get high productivity, but to provide the best quality system possible. The welding power supply executes the weld parameters with a high degree of accuracy weld after weld. It is up to the installing contractor and his operators to control other factors that could affect weld repeatability. The welding operators received training in operation of the equipment and are proficient at developing weld schedules for each size of tubing and know how to cope with heat-to-heat variation in weldability. Installing contractors have developed Standard Operating Procedures (SOPs) detailing every aspect of the orbital welding process.

ASME BPE Standard

Sicor Inc. hired a third-party QA company to inspect their welds. In addition to weld procedure qualification to ASME Sect. IX and B31.3³, inspectors used the visual criteria for weld acceptance from the Materials Joining part of ASME Bioprocessing Equipment Standard (BPE-2002).¹ The BPE Standard was originally published in 1997 and was revised in 2002. The BPE Standard was the first standard written for the biopharmaceutical industry that specifically recommends the use of orbital welding.

The Dimensions and Tolerances (DT) Part of the BPE Standard has contributed to improved consistency of orbital welding by specifying acceptance criteria for wall thicknesses and ovality of weld ends of fittings and other components for bioprocess systems. Since the welding current for orbital welding is roughly proportional to wall thickness with about 1 amp of welding current for each 0.001 inch, a variation of more than a few thousandths of an inch in wall thickness could make a difference in weld bead penetration. Similarly, the squareness of the weld end is controlled so that there will be no significant gap between parts when secured in the weld head. Good fit-up and alignment of parts for welding is essential.

The material generally used in high purity biopharmaceutical applications is 316 or 316L stainless steel.⁶ For welding, the reduced carbon content of 316L is preferred. With higher carbon levels (0.080 wt.% in 316 compared to 0.035 wt.% in 316L), there is a chance of carbon migrating to the grain boundaries in the area immediately adjacent to the



Figure 3. Video borescope display showing I.D. weld bead from a field weld and information recorded for each weld. Photo courtesy of Purity Systems, Inc.

weld during welding, combining with chromium and precipitating as chromium carbide leaving the grain boundaries in the Heat-Affected Zone (HAZ) reduced in chromium, and thus subject to intergranular corrosive attack. However, since the formation of chromium carbide is time and temperature dependant, the precisely controlled heat input of orbital welding makes this occurrence less likely than with manual welding.

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In the interest of weldability, the DT Part of the BPE standard has limited the sulfur range of type 316L stainless steel used for fittings and weld ends of components to 0.005 to 0.017 weight% and recommends the use of tubing specified to ASTM A270 S-2 Pharmaceutical Grade which has the same sulfur range as the BPE. This is in contrast to the AISI specification which lists a maximum sulfur concentration of 0.030 weight%, but no minimum. Heat-to-heat variation in base metal chemistry of stainless steels results in differences in weldability and is a major cause of weld inconsistency. The limited sulfur range has eliminated much of the uncertainty in fabrication and greatly increased the consistency of orbital tube welding for those using this standard.⁷

When materials arrive on site, they are received and logged by the installing contractor and then inspected and logged by third-party QA. ASME B31.3 Process Piping Chapter VI distinguishes between *examination* and *inspection*. *Inspection* applies to functions performed for the owner by the owner's inspector or the inspector's delegates (QA), while *examination* applies to quality control functions performed by the manufacturer, fabricator or erector, in this case the installing contractor (QC). Weld criteria are detailed in the Materials Joining part of the BPE Standard.

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