Boston Area Chapter

Boston Area Chapter Newsletter

February 2004 Volume XIIII, Number 1

Boston Area Chapter Holiday Social

The Boston Area Chapter Annual Holiday Social and TOYS for TOTS Benefit was held December 3rd at Jillian's in Boston.

Nearly one hundred members from the local Chapter met in a private room complete with hors d'oeuvres and pool tables. The evening was more than just fun because the event raised nearly $600 in cash and numerous toys for the TOYS for TOTS charity. The Boston Area Chapter has teamed with the USMC for several years at this event to support this worthy cause.

Volunteers present from the USMC were Gunnery Sergeant Robert Alexander Jr. and Corporals Brian Wheelock and Steven Whitney.

Process Piping Documentation for Pharmaceutical and Biotech Applications

Tim Paulding,GMP Systems Inc.

Introduction

Process piping systems are critical components of pharmaceutical and biotech development and manufacturing facilities, transporting raw materials, intermediate and final products, and utilities from one location or piece of equipment to another. Because process piping systems are often in contact with product materials, proper fabrication and installation, along with supporting documentation, are important considerations in the construction and operation of a pharmaceutical or biotech facility. This introductory article provides an overview of the type of documentation that should accompany the installation of a process piping system.

In order to fully satisfy the product quality requirements in the pharmaceutical and biotech industries, process piping systems must meet several requirements. First, the piping systems must adhere to the engineering design specified by the user group or owner. Second, the installation and documentation must be completed in a manner consistent with current Good Manufacturing Practices (cGMPs). Lastly, the piping must meet applicable sections of one or more ASME codes and standards (depending on the specific application):

- Process Piping Code (B31.3-2002)
- Boiler and Pressure Vessel Code
- Standard for Bioprocessing Equipment (ASME BPE-2002)

The documentation necessary to meet these requirements is normally divided into four distinct categories, each covering a specific aspect of piping system installation and commissioning:

- Piping Components
- Joining Methods
- Welders or Welding Operators
- Examination and Testing

Each of these four categories is discussed below. In all cases, responsibility for complete and accurate documentation rests with the installer of the process piping system, generally the owner or a specialized installation contractor.

Piping Components

The piping installer must provide detailed documentation verifying that the piping system components (tubing, fittings, valves, etc.) meet the requirements established in the system design specification. At a minimum, this documentation consists of the following:

Continued on page 4.

MYCOPLASMA REMOVAL/LIQ NITROGEN FILTRATION

ISPE Boston Area Chapter - January 8, 2004

The Boston Area Chapter program for the January meeting covered two sterility related topics. James Blackwell of the Abbott Bioresearch Center discussed Removal of Mycoplasm from Cell Culture Media by Filtration and Leesa McBurnie from Meissner Filtration Products spoke on the Validation of Sterile Filtration of Liquid Nitrogen.

Mycoplasma is a common contaminant of mammalian cell cultures. Mycoplasma are parasitic microorganisms possessing some characteristics of both bacteria and viruses. With no cell wall they can change shape easily and can be smaller than 0.2 µm in diameter. Their effect on cell cultures can be unpredictable as mycoplasma can alter nucleic acid metabolism and cause chromosomal aberrations. Of the over 100 species of mycoplasma six account for more than 90% of contaminations. Three of these six are found in humans *M. orale*, *M. fermentans* and *M. hominis*. Mycoplasma are very sensitive to heat and can be killed in a very short period of time by heat sterilization or can be removed by filtration using 0.1 µm filters.

There are currently no regulatory standards for 0.1 µm filters. Abbott performed a series of tests on six different types of filters to evaluate the removal of mycoplasma. The Abbott experiments were performed at 60 psig with the addition of Pluronic F-68 surfactant and a challenge by *A. Laidlawii* of greater than $1x10^7$ cfu/ml. Three filters from different vendor lots of each of the six filter types were tested. The filter types were two 0.1 µm PVDF, two 0.1 µm PS (polyethersulfone) and one 0.04 µm PS and one 0.01 µm Nylon.

The test results showed Log Reduction Values ranging from 5.8 to 8.78. None of the filters were completely retentive for 0.1 mm organisms as even in the best test one organism was detected; in the worst case 470 organisms were detected. Abbott's tests also showed that there was a significant difference in the performance of different filters and that anisotropic filters performed better. Abbott found guidance from existing literature and vendors lacking and their test cast doubt on vendors' claims of 100% retention of 0.1µm organisms, as their qualifications may not be applicable under different operating conditions.

Liquid nitrogen is used throughout the pharmaceutical industry for storage of microbial cultures, lyophilization baths and the quick freezing of pharmaceutical preparations. There have been contamination problems linked to liquid nitrogen for example a 1995 outbreak of hepatitis B in patients undergoing cytotoxic treatment. Also, *Aspergillus* and bacterial contamination were found both in freezers and the cultures stored in them and *Bacillus* has been found in liquid nitrogen storage containers.

To reduce the potential for contamination liquid nitrogen can be sterile filtered, however at –196°C it is below the normal operating limits of most filters. PTFE becomes less brittle at low temperatures than other commonly used plastics such as PES, PVDF, nylon and polypropylene. The extreme temperature variations between steaming and filtering liquid nitrogen can create problems with the different materials of construction in filters due to different coefficients of thermal expansion. For example SS reinforcement rings can break the plastic adapter after freezing. Plastic rings are preferable.

Tests were performed to validate the filter sterilization. The filters used were PP structure with PTFE membranes (1 sq. ft.). Filters from three lots underwent steam sterilization at elevated temperatures (134°C to 145°C). Liquid nitrogen (5 L) was then passed through the filters and the process repeated two more times. The filters were integrity tested and then challenged with *Brevundimonas diminuta*.

All the filters passed the integrity and bacterial challenge tests. Additional data was collected on two filters that were subjected to six sterilization/filtration cycles. In the post use integrity test one of these filters showed a bubble point below manufacturer's specifications and also failed the bacterial challenge.

The tests showed that liquid nitrogen could be successfully sterile filtered with PTFE cartridges. It is important to integrity test filters before and after use. It is recommended to use filters only once although up to three cycles is probably acceptable.

Lonza Plant Tour

The Lonza Plant tour took place on December 9, 2003 in Portsmouth, NH. Lonza is company which offers "custom manufacturing for chemical synthesis, microbial fermentation, and mammalian cell culture[1]." The discussion topic was "Facility Design from a Maintenance, Repair, and Shutdown Prospective: Pay Me Now or Pay Me Later."

Steve Kennedy (Process Facilities Inc.) and John Machulski (Lonza Biologics) were the presenters. They discussed the issues involved in building a manufacturing facility. They covered the building concept, facility design, contamination control, and containment strategies. They also described the utility systems, finishes for equipment, floors, and walls, and building materials.

Following the thorough and interesting discussion, several groups were guided throughout the plant. The new manufacturing facility was amazing. The technology was state of the art.

The construction, planning, and engineering teams have built an outstanding addition to the Lonza Biologics facility.

1 Source is Lonza Custom Manufacturing Brochure

Monique Sprueill

Member's Spotlight

Let's all look forward to meeting Ms. Jodi Day of Biogen Idec, one of our newest Chapter members. Day is "still discovering all that ISPE, and our local Chapter, have to offer." She is most interested in networking opportunities. She is currently taking the certification classes for GMP auditing and hopes to continue her training. She will soon begin taking a class on CFR Part 11 compliance.

Day's enthusiasm for the sciences dates back to middle school in Albany, NY. Her early interests were in earth sciences and meteorology. In her junior year of high school she focused on biology and chemistry, enjoying them along with physics. She imagined a career in research. This led Day to major in biology and minor in chemistry at Le Moyne College, Syracuse, NY, from which she graduated with a Masters Degree in Science.

Day decided to move to Boston "to see where my degree would take me." She started with Biogen nearly five years ago, doing quality Control work in chemistry. It proved to be an experience compatible with her interest in the sciences and assured her of the considerable opportunities in an industrial setting. She is now a Quality Assurance Specialist with Biogen Idec, and the first in her family to pursue a career in the sciences.

We wish Day great success in her career and encourage her to take full advantage of what our Chapter has to offer.

Process Piping Documentation for Pharmaceutical and Biotech Applications (cont.)

- **Submittals -** detailed specifications describing each component with signatures indicating acceptance by the owner or owner's representative
- **Certificates of Compliance and/or Mill Test Reports -** lot-specific documentation provided by the component manufacturer certifying that the components supplied meet the specifications contained in the submittals
- **Incoming Quality Control Reports -** containing the results of incoming QC inspection performed by the installer or a third-party employed for this purpose

Joining Methods

The piping installer must provide complete documentation describing the joining methodology used in the assembly of a process piping system as described in applicable sections of the Process Piping Code and Section IX of the Boiler and Pressure Vessel Code.

As an example, the joining-method documentation for a purified water distribution system constructed of 316L stainless steel would provide a detailed description of the GTAW (Gas Tungsten Arc Welding) process, consisting of the following:

- **Welding Procedure Specifications (WPS) -** defined in Section IX of the Boiler and Pressure Vessel Code, the WPS is a written document that provides direction to the welder (or welding operator in the case of automatic welding) for making production welds in accordance with Code requirements. The WPS fully describes the GTAW process used to assemble the system. Form QW-482 included in Appendix B of Section IX may be used as a model for the WPS.
- **Procedure Qualification Record (PQR) -** the PQR certifies that test welds performed in accordance with the WPS meet Code requirements and summarizes the specific test results. Form QW-483, also found in Appendix B, may be used as a model for the PQR.
- **Weld Map -** an isometric drawing showing the location and numerical identification of each weld used in the construction of a process piping system. Each weld, when completed, is labeled with the weld number indicated on the weld map, the date completed, and the welder/welding operator identification number or code.
- **Weld Log -** the weld log contains critical data pertaining to each weld identified on the weld map, including the results of in-process examinations.
- **Weld Sample Coupons -** actual test welds used to demonstrate weld quality at critical points during system installation. At a minimum, test welds are performed at the beginning of each shift, before and after "blind" welds, and whenever a significant change is made (replacement of electrode, purge gas, power source, etc.) that may affect weld quality.

Welders and Welding Operators

The piping installer is responsible for the performance of welders/welding operators and must provide documentation establishing the individual welder/welding operator's ability to create welds in accordance with the WPS and Code requirements. This documentation consists of the following:

- **Welder/Welding Operator Performance Qualification (WPQ) -** The WPQ documents the results of performance testing as required by Appendix B Section IX. Forms QW-484A and B included in Appendix B of Section IX may be used as models for the WPQ for welders and welding operators, respectively.
- **Identification of Welders and Welding Operators -** Each qualified welder and welding operator must be assigned a unique number or code that is used to identify individual work.

Examination and Testing

Tests and examinations applied to process piping systems are used for two purposes:

- During system installation, to verify the quality of individual welds, system cleanliness and other key design parameters, such as line slope
- When installation is complete, to verify overall system integrity

Using the prior example of a purified water distribution system, in-process testing would consist of visual examination of the external surface of all welds, borescopic examination of internal surface of selected welds, acceptance (or rejection) of each weld, any additional testing agreed upon by the owner and installer, and the completion of associated documentation. Process piping systems subject to more rigorous operating conditions may be subject to additional examination and testing requirements.

Once installation is complete, the installer completes a final hydrostatic or pneumatic leak-test to verify overall system integrity. The test must be performed and documented according Section 345 of the Process Piping Code.

Both in-process examination and leak testing are the responsibility of the installer and must be conducted and documented by qualified personnel according to written procedures. However, it is the owner's ultimate responsibility to verify that the required testing and examinations have been conducted and that the system, as installed, conforms to Code and to the requirements of the engineering design.

Tim Paulding is Vice President and Project Manager for GMP Systems, a process piping contractor based in Lowell, MA.

Rouging in Stainless Steel Equiment

Richard E. Avery, Edited by: Pietro Perrone

Introduction

Stainless steels are one of the most versatile and widely used materials for domestic and industrial use. The pharmaceutical industry makes extensive use of Type 316L equipment. However, when material performance questions arise and rouging of stainless steel in high-purity water systems occurs, the causes are not well understood. Industry does not have all the answers on rouging. This brief overview presents some new work that helps in identifying factors for rouging. Identifying these factors should help in minimizing the occurrences of rouging in stainless steel systems.

What is Rouging?

Rouging is a term used to describe deposits that form in stainless steel systems. The rouge can vary in color from a light-red to reddish-brown and to dark violet or black deposits. The particles that make up the deposits have been identified as predominately one of the species of iron oxide. Rouge can be in the form of a loose film that can be easily wiped off or a very tenacious film that is difficult to scrape off. Tverberg and Ledden have identified three classes of rouge. [1]

- Class I Rouge - Iron oxide particles originating elsewhere and deposited downstream. The stainless steel surface and the Cr/Fe ratio of the metal surface beneath such deposits usually remain unaltered.
- Class II Rouge - Iron particles originating in-situ on unpassivated or improperly passivated stainless steel surfaces. By their formation the Cr/Fe ratio of the metal surface is altered.
- Class III Rouge - Iron oxide (or scale) which forms on surfaces in high temperature steam systems. The Cr/Fe ratio of the protective film is usually altered.

Rouge deposits can develop in a number of locations in a high purity water system and the deposit is not limited to stainless steel surfaces. Rouge deposition seems to have an affinity for Telfon® and should be one of the first places to look for signs of system rouging. [2]

Factors Influencing Rouge Formation

A number of factors may contribute to the formation of rouge in a high-purity water system. In recent work rouge was produced in the laboratory on 316L exposed to WFI and purged with different gases. [3] Rouge developed faster when WFI was purged with nitrogen and synthetic air containing plus 1^{+}% CO_2. Little or no rouge developed in synthetic air or de-carbonated air.

Different stainless steel surfaces have an impact on rouge formation. In addition to a sheet mill finish, there are various surface treatments that can be done to stainless steel components. These include mechanical polishing, electropolishing and passivation. These treatments typically have an effect on rouge formation. In unpublished work sponsored by Nickel Development Institute, the iron release rate (which in turn could be a source of rouge) in ultra-high purity water was measured. Some of the findings were:

- mechanically polishing to a 180 and 360 grit finish resulted in an iron release over three times that of an undisturbed 2B finish
- iron release from the 2B finish was reduced to a nil amount by a nitric-hydrofluoric acid pickle or nitric acid passivation
- a properly performed electropolish followed by a nitric acid passivation resulted in nil iron release

Pumps in stainless steel systems may also contribute to downstream rouge deposits. The iron release might be the result of impeller erosion due to excessively high tip speeds or from cavitation.

The presence of an alloy with a lower corrosion resistance than 316L often increases rouge formation. An example of this is a straight chromium stainless steel component in a high purity water system.

Is Rouge a Forerunner to a Corrosion Failure?

The iron that forms the iron oxide rouge particles in a total stainless steel system originates from the stainless steel. The amount of iron released is small and is generated from a large surface area. Therefore the material thickness reduction is considered insignificant. An exception to thickness reduction might be at pumps previously mentioned. Additionally, there is no proof that rouge formation promotes pitting or crevice corrosion.

The possibility of rouge adversely affecting products being processed has been raised. Opinions vary on this point, since it is influenced by factors such as the amount and form of rouge and the products being processed. However, the prudent practice would be to prevent or minimize rouge to the extent possible and when not possible, de-rouge and passivate as needed.

Concluding Remarks

This brief overview on rouging and the factors that contribute to its development in stainless steel equipment provides an introduction to this topic. When rouging is identified in a stainless steel system, there are de-rouging and passivation treatments available for fully restoring the stainless steel surface.

References

1 *Tverberg, J. C., and Ledden, J. A., "Rouging of Stainless Steel in WFI and High Purity Water Systems," Proceedings of Tube 2000, Dusseldorf, 2000.*

2 *Banes, P. H., "Materials - Fundamentals of Passivation in Water Systems," Ultrapure Water, April 1998.*

3 *Mathiesen, T. et al, "Using Exposure Tests to Examine Rouging of Stainless Steel," Pharmaceutical Engineering, July/August 2002.*

NEWSBRIEFS IN BIOTECHNOLOGY

Merck Submits NDA for Arcoxia

Arcoxia is a drug used to treat osteoarthritis, rheumatoid arthritis, acute pain and ankylosing spondylitis. The initial application was withdrawn in 2002 as the possibility to treat a spinal inflammatory condition was explored.
(Source: Datamonitor Newswire, 5 January 2004)

US Veteran Affairs Changes Drug Wholesaler

The new prime wholesale vendor for the VA is McKesson. As of April 1st, Amerisource Bergen will no longer service the VA.
(Source: Datamonitor Newswire, 5 January 2004)

Trinity Biotech's Uni-Gold Recombinant HIV Test Approved by FDA

This product can be used to detect HIV in Human serum, plasma, or blood. 9,000 patients were tested using this method, which produces results in less time.
(Source: Datamonitor Newswire, 5 January 2004)

Eli Lilly Predicts 10% Sales Increase This Year

This company anticipates increased sales after launching six new products. This increase in funds will be used to support research efforts.
(Source: Datamonitor Newswire, 6 January 2004)

GSK Enters Licensing Agreement with SkyePharma

GSK has partnered with SkyePharma to access technology that will be used respiratory drugs. This will facilitate the release of products, which will be delivered through breath-actuators and metered dose inhalers.
(Source: Datamonitor Newswire, 6 January 2004)

Monique Sprueill

New Members

Frank Armstrong, QA Manager
Cotter Brothers Corp
David G. Brush, Sr. Process Engineer, PFI
Charles L. Choi, PFI
Michele R. Cohoon, Technical Svc Engineer, The Chisholm Corp
Randolph A. Cotter, Jr. President, Cotter Brothers Corp.
Timothy J. Cotter, Vice President, Cotter Brothers Corp
Cheryl A. Crosby, Technical Project Assistant, Perceptive Informatics
Brenda J. Davulis, Project Specialist, Wyeth BioPharma
Richard Engler, Vice President E & S Technologies Inc.
Joseph M. Ferrelli, Regional Sales Mgr, Optek
Christopher P. Foran, Project Engineer, Superior Controls Inc.
Richard J. Greer, Jr., QVM Services Inc.
Michael D. Hodgdon, Supervisor, Wyeth BioPharma
James J. Hoefner, VP, General Manager, TEK Supply Inc.
Michele A. Holmes, Exhibits Coordinator, Millipore Corp.
David W. Leavitt, Senior Project Manager, Cianbro Corp.
Stephen Lenhart, QA Senior Compliance Specialist, Genzyme Corporation
Eric J. Mulder, Engineer Abbott Bioresearch Center
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Robert A. Patrick, Project Manager Superior Controls Inc.
Rudy Rumohr, Jr., Director, Systems Operations Sepracor Inc.
Steven Schwertz, Validation Specialist Masy Systems Inc.
Matthew J. Stafford, Project Engineer Superior Controls Inc.
Cheryl Stearns, Facilities Engineer Biopure Corp.
Lauren J. Sykes, Validation Specialist, Massachusetts Biologic Labs
Annette Torres, Systems Analyst, Wyeth Biopharma
Mark J. Tschirch, Regional Sales Manager, Clark-Reliance Corp.
James A. Watson, Process Engineer, Integrated Process Technologies
Freeman A. Wilson, General Manager Cotter Brothers Corp.

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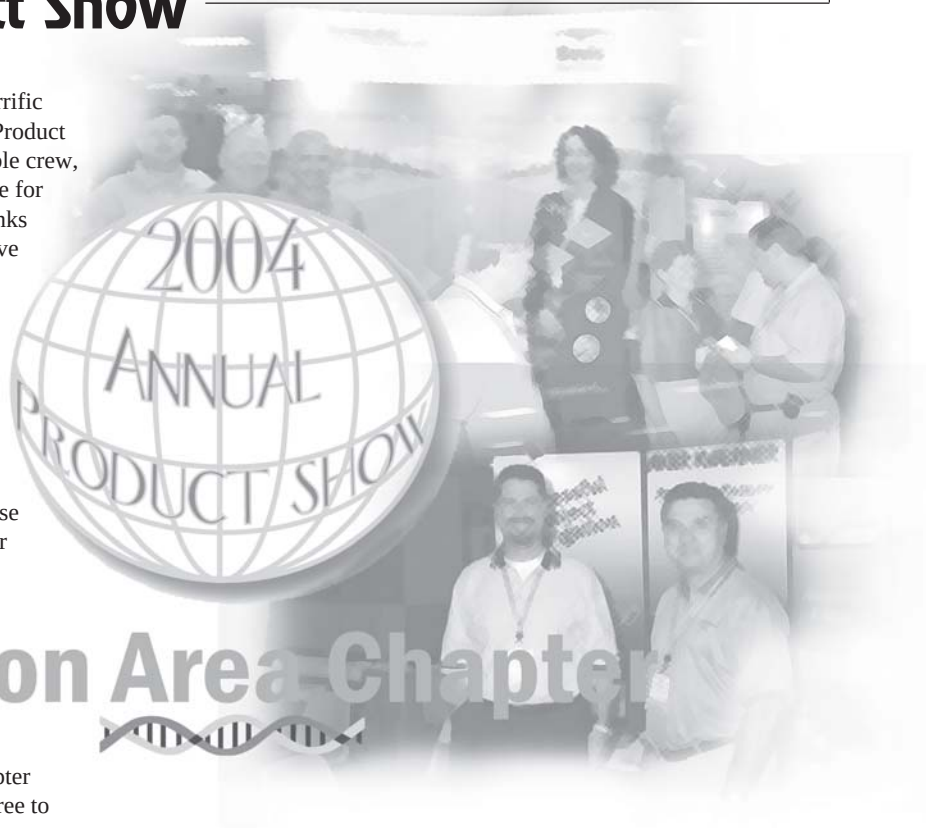
2004 Annual Product Show



Our Chapter and membership once again enjoyed a terrific turnout of more than 530 attendees for the Annual Product Show. Special thanks go to Jim Grunwald and his able crew, who put together a fine program of speakers, adding incentive for many to attend and visit the vendor displays. Also, many thanks go to the volunteers handling the registration tables. They gave a very good impression to the many vendors and attendees.

The food and drinks available were excellent, as was the service provided by the hotel. Very good choices were made all around.

This is perhaps the premier networking event of the year for our Chapter's members. More information can be gathered in a shorter period of time and with less effort than any other such affair in our industry. It is nice that so many members realize the advantages offered by the Chapter and use these events to seek out information, helping them attain their goals.

Jim Berry is chairperson for future Product Shows. Berry and his expanding group of volunteers are already planning to further enhance the show, scheduled to take place in November 2004.

The chairpersons for the Product Show and all other Chapter activities appreciate feedback from participants. Please feel free to contact them directly, or through CAMI.

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