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Applying Predictive Maintenance Techniques to Utility Systems

by Padraig Liggan and David Lyons

This article discusses how Predictive Maintenance (PdM) technologies can be successfully applied to both GMP and non-GMP utility systems in the pharmaceutical industry. The discussion also demonstrates the clear benefits of PdM, including the use of a proactive approach to maintenance.

Introduction

Pharmaceutical production is one of the most heavily regulated industries. With such an emphasis on product quality within the industry and with such economic and health consequences due to machine failure, the maintenance team plays a crucial role in the success of the product. It is the maintenance department's responsibility to ensure equipment is kept to its maximum operating condition. It must predict and prevent failures and repair any problems which may already have led to a failure, while adhering to the rules and procedures set out by the respective regulatory bodies. In addition, critical GMP utility systems supporting production are qualified and associated documentation is needed to prove that equipment serves its function consistently as per the design.

This often leads to maintenance departments performing more work than is necessary to increase assurance of equipment reliability, even if these extra precautions do not necessarily provide any additional benefits.

During the qualification of these systems, the maintenance program is developed and put in place. To change the content of maintenance after this can prove difficult as strict change control procedures often need to be followed and full documented justification needs to be provided. This can sometimes lead to maintenance programs being left as is and the opportunity for continuous improvement missed.

In recent year's, regulatory agencies such as the US Food and Drug Administration (FDA) and the Irish Medicines Board (IMB) have become more supportive of emerging modern maintenance techniques. Tools such as Reliability Centered Maintenance (RCM) and the use of the many sciences involved in Predictive Maintenance (PdM) are seen as a way of improving the maintenance function. This is allowing pharmaceutical companies to become more cost competitive while still ensuring utmost quality to the pharmaceutical products end user: the patient.

What is PdM?

Most modern industries are moving toward a 24/7 production schedule; the supporting equipment and systems availability need to keep up. No longer do maintenance departments have the luxury of extended periods of available equipment downtime in order to carry out maintenance, instead the maintenance function is moving toward a more predictive approach. This is where the modern technologies of PdM are now predominately being used to effectively monitor performance of equipment and plan maintenance interventions in a timely manner.

PdM is a group of emerging scientific technologies that can be employed to detect potential failures that may not be evident through a preventative maintenance program. If the failure characteristics of the equipment are known, PdM can detect the failure well in advance and appropriate actions can be taken in a planned manner. The use of condition based maintenance has dramatically reduced non-value added maintenance by eliminating the need to unnecessarily shutdown equipment for maintenance checks. Some of the main technologies currently used in industry are listed below:

- Thermography – infra-red imaging to detect abnormal temperatures or hot spots.
- Vibration monitoring – accelerometer instruments can be used to detect abnormal or high vibration particularly in bearings.
- Oil analysis – sampling of oil (which is then analyzed) can detect the deterioration or breaking down of an internal equipment part.

PdM Technique	Applications			
Vibration Analysis	Rotating Equipment/Drive Systems	Structural Vibration	Motors	Fan Balancing
Oil Analysis	Component Wear and Tear	Oil Degradation	Water Ingress in Oil	Equipment Overheating
Ultrasonic Detection	Steam Trap Testing	Leak Detection	Electrical Arcing	Valve Integrity
Thermal Imaging	Electrical Overheating	Steam Trap Testing	Mechanical Overheating	Insulation Checks

Table A. Typical utility system applications for PdM.

- Ultrasonic measurement – use of ultrasound technologies to detect leaks or blockages on utility systems.

PdM is a relatively new science and has clear benefits in the industry; however, there is a danger of relying too much on these technologies. There must be a fine balance between PdM and conventional maintenance practices.

"Is predictive maintenance a burden or benefit?"[1] PdM will give maintenance personnel ample warning of a potential failure, but may take the focus away from the actual root cause of the failure. For a truly effective predictive maintenance program, a balanced cost (based on the risk and consequence of equipment failure) should be spent on PdM, but also it should only be used as a first step into determining why the equipment being monitored is starting to fail and what are the possible contributions.[1] This is where the experienced maintenance professionals are still an important part of the maintenance process.

This article will present four of the main types of PdM that can be applied to the maintenance program for GMP critical utilities and also highlight the results an organization can hope to achieve.

PdM – an Overview of the Applications and Benefits

Predictive maintenance has become a key part of the modern maintenance department and more and more companies are taking on board these technologies in order to maximize the reliability of their equipment by detecting failures well in advance. Some failure modes cannot be designed out (i.e., mechanical bearings are here to stay, electrical panels will always be an integral part of any system), but if failures can be detected early, the maintenance team can plan the work in an organized manner. Unplanned breakdown maintenance can cost as much as three times that of planned maintenance[2] so PdM is of significant benefit. Detecting a failure early means that the level of damage that can follow an actual failure also can be avoided or reduced. An example would be when a bearing failure occurs on an air handling unit fan, this can have disastrous consequences on the internals of the fan, which may start breaking up and the fan shaft may become damaged beyond repair. If this example was to be presented in terms of cost only:

- Case 1 (with PdM) – potential bearing failure is detected using vibration analysis, replacement cost of bearing ~ $100's
- Case 2 (without PdM) – no vibration analysis program, catastrophic failure of fan bearing causing fan impellers to break and the shaft is beyond repair, cost of new fan ~ $1000's + cost of downtime to manufacturing.

Companies often choose to initially outsource predictive maintenance services and then invest over time for internal training on the techniques and the purchasing of equipment. Either way, it is clear that PdM can pay for itself many times over and this is why it is becoming so popular. Table A gives a high-level overview of typical utility system applications for PdM.

Vibration Analysis

Vibration Analysis Principles

Vibration can be defined as simply the cyclic or oscillating motion of a machine or machine component from its position of rest. It is normal for all machines to have some level of small vibration; however, when this vibration increases or becomes excessive, it usually indicates a mechanical fault of some description. Vibration analysis uses accelerometer instruments to detect these vibration movements, the results of these vibration readings can be plotted (magnitude Vs frequency) using a mathematical representation called Fast Fourier Transform (FFT). The FFT plot will highlight the level of vibration and identify which frequencies they are present in. The frequencies present are related to the machine cyclic movement, such as RPM, and by using this data the origin of the fault can be determined.

Figure 1 shows a typical vibration plot for a motor drive unit, the different frequencies present relate to the different moving components within the drive unit. Each element in the drive system operates at different frequencies and the magnitude of the vibration is used to determine if a fault exists. The vibration levels or magnitude levels also will tell the vibration analyst how severe the vibration is and whether any action is needed. It is common in industry to take a set of

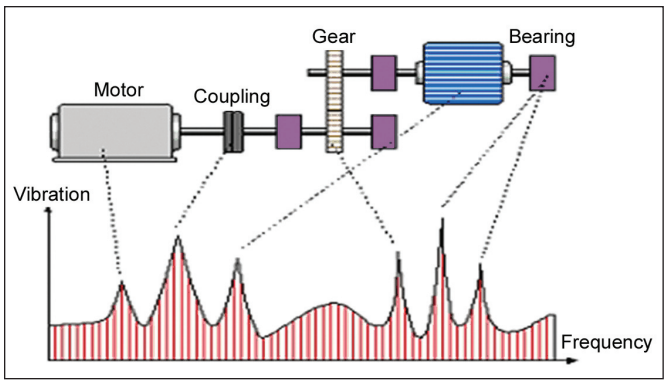


Figure 1. Typical vibration analysis FFT plot (magnitude vs. fequency).

baseline readings when the equipment is first installed, the condition of the equipment can then be trended over time and areas of deterioration can be identified. Vibration analysis is quite a complex subject and takes a lot of mechanical expertise and training in order to become proficient. The vibration analysis plots can often contain multiple fault frequencies and in order to determine their origin, the analyst needs to have detailed knowledge of the operating characteristics of the equipment (such as number of fan blades, RPMs, pulley ratios, bearing types, etc.). For this reason, false diagnosis can sometimes be a problem. With the correct training and mechanical proficiency, the following types of problems can be determined using vibration analysis:

- misalignment of drive systems
- unbalance of rotary components
- mechanical looseness
- bearing deterioration and gear wear
- belt deflection

As mentioned above, accelerometer instruments are used to detect levels of vibration. These instruments can be used in the following ways in order to collect the data:

- The accelerometer instrument is placed manually on the selected equipment location. The data is collected onto a storage device for further analysis using computer software. These storage devices known as "vibration analysis data packs" also allow some basic analysis to be completed at the equipment being measured.
- Accelerometer instruments are fixed to the selected equipment location. The readings are taken at specified intervals and analyzed further. (This is particularly useful for difficult to access locations such as continually operating enclosed drive systems.)
- Accelerometer instruments are fixed to the selected equipment location and are also connected directly to a plant management software system, such as Distributed Control System (DCS). These accelerometers also can be connected to wireless data sending devices which allows remote monitoring and analysis to be carried out.

The following is an example of data that is required to setup an initial vibration analysis program for a complex rotary drive system:

- motor rating (KW)
- RPM
- motor non drive end bearing type
- motor drive end bearing type
- fan/pump drive end bearing type
- fan/pump non drive end bearing type
- driver pulley size
- driven pulley size
- belt length and number of belts
- gearbox ratio
- pump/fan vanes (number of)

PdM Type	Program	Frequency
Vibration Analysis	- 228 Pumps - 124 Air Handling Units - 138 Extract Fans - 9 York Chillers - 9 Atlas Copco Compressors - 6 Cooling Towers - On Demand - Following Repairs	3 Months

Table B. Sample vibration analysis program.

- base vibration levels (to allow trending)

Vibration Analysis – Practical Applications

Table B shows a sample vibration analysis program for a large pharmaceutical manufacturing site and the type of equipment typically covered. Note that for utilities equipment operating 24/7, the vibration analysis inspection intervals for bearings are typically three months. The reason being that, the P-F interval for a bearing (P-F means from the point the failure is detectable to the time of failure) is typically around four months. By inspecting at three monthly intervals, the VA program is more likely to detect bearing failure onset before becoming catastrophic. P-F intervals can vary for different types of components with wear-out operational characteristics; the probability of detecting the onset of a component failure is increased by ensuring the PdM inspection interval is less than the P-F interval.

Thermal Imaging

Thermal Imaging Principles

Thermal imaging uses Infra-Red (IR) technology to identify high temperature areas on the surface of equipment. Thermal imaging is used primarily on electrical panels to identify loose contacts or overheating of cables, but there are other ranges of applications, such as checking for blockages in pipes or carrying out heat surveys in plant rooms. Typical equipment used is an infra-red camera which can range in cost from $10,000-$40,000 and usually comes with a software package to load, store, and compile results. Use of the infra-red camera requires specific training as setting up of the camera and interpretation of results requires a level of expertise. It is better to have an electrically competent person carrying out thermal imaging surveys as the causes of faults particularly in electrical panels can be diagnosed straight away giving the maintenance team useful information before carrying out repair works. It is important to note that infra-red imaging requires a direct exposure to the surface being measured; infra-red cannot penetrate through surfaces, such as glass or plastic, unless specifically designed IR windows are installed. When setting up the IR camera the emissivity factor (ε) is an important parameter. Emissivity is a heat factor which allows for the material type being scanned, its color and the angle of heat being radiated. A true black body would have an emissivity factor of $\varepsilon = 1$ with other surfaces being less $\varepsilon < 1$. Its value is important because if not set correctly, the true temperature reading could be offset; there are ranges of emissivity settings available for common types of material, such as PVC coated cables in electrical panels.

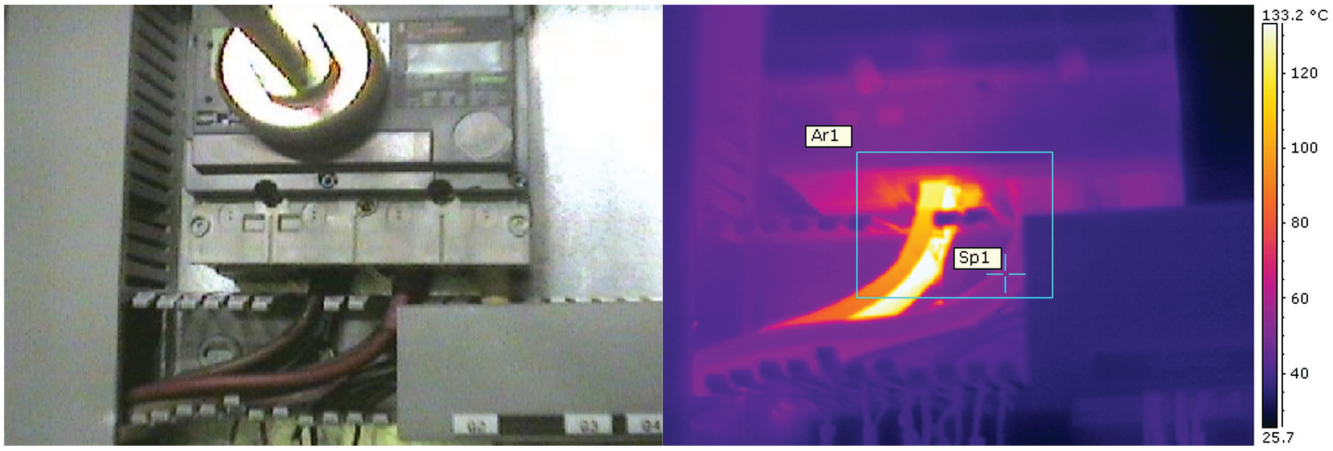


Figure 2. Thermal image of an electrical isolator.

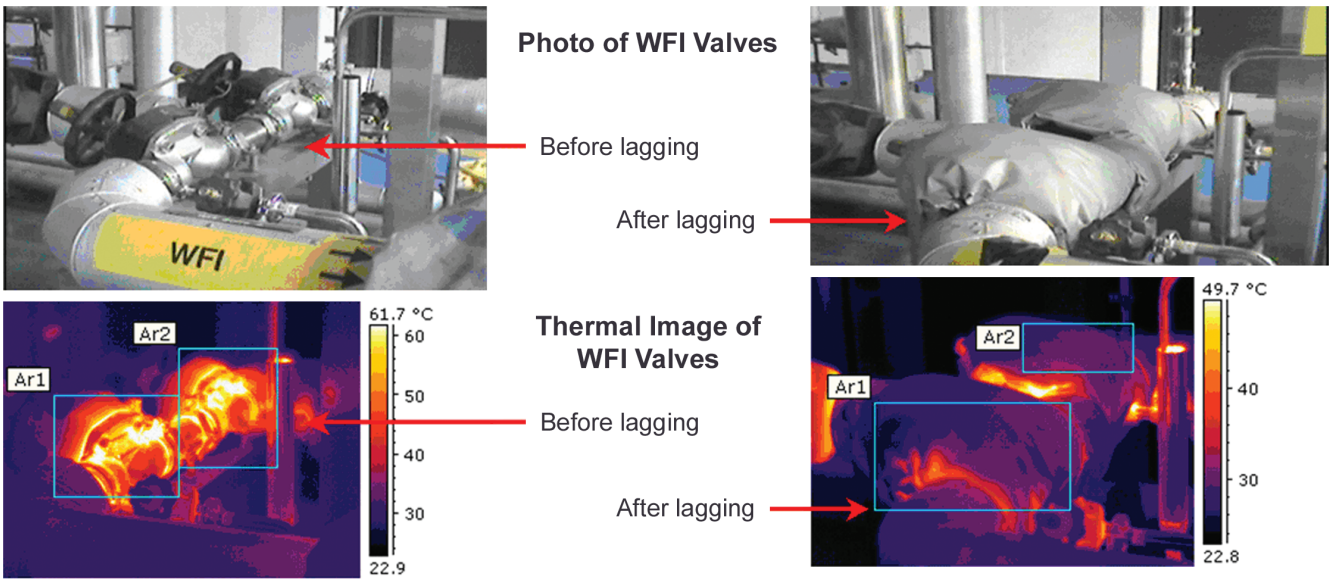
Thermal Imaging – Practical Applications

Figure 2 shows a thermal scan of a cleanroom air handling unit electrical isolator taken in 2007, the top left photo shows a normal exposure and the shot on the right is a thermal image. This particular fault was severe with a maximum temperature of 133.2°C (271.8°F).

The fault, found on the incoming cables, was due to internal deterioration of the cable and was creating excessive heat. A condition like this unattended over time would eventually cause the equipment to fail and possibly lead to fire. Once the maintenance team are notified, this fault can be repaired by replacing the cables and ensuring all connections are secure. The repaired panel is then rescanned to ensure that the fault no longer exists.

As mentioned at the beginning of this section, there are other applications that thermal imaging can be used. In 2006, due to concerns of excessive heat in a plant, it was decided to carry out a thermal scan of the area utilities to identify hot spots which could then be insulated and help reduce overall heat levels in the plant room.

Figure 3 shows a thermal scan of a clean water system's pipework and valves, showing temperatures of approximately



Object Parameter	Value
Emissivity	1.00
Label	**Value**
Ar1: Max	72.4°C
Ar2: Max	69.4°C

Object Parameter	Value
Emissivity	1.00
Label	**Value**
Ar1: Max	42.2°C
Ar2: Max	32.9°C

Figure 3. Thermal image survey of utility pipework.

70°C (158°F). Following lagging of the identified pipework and valves, the temperature was reduced by around 30°C (86°F). This survey was carried out for the entire plant room and identified numerous areas of equipment where excessive heat was being given off and contributing to the overall high temperatures in the plant room. This also led to efficiencies in terms of energy costs.

Thermal imaging can be readily applied to the following general categories of electrical distribution boards:

- small low voltage (220 to 380V) panels (i.e., miniature circuit breaker boards)
- large low voltage (220 to 380V) panels (i.e., motor control centers)
- medium voltage (<1000V) switchgear panels

Table C shows the sample array of equipment on the thermal imaging program for a large pharmaceutical manufacturing site.

PdM Type	Program	Frequency
Thermal Imaging	- 33 MV Transformers/Associated Switchgear - 43 Motor Control Centers - 205 MCB Panels - 316 Frequency Drives - 22 UPS Panels - 88 Process Panels - Fabric/Roof Membrane Inspection - Insulation Inspection - On Demand - Following Repairs	12 Months

Table C. Sample thermal imaging program.

Oil Analysis

Oil Analysis Principles

Oils, greases, and other lubricants are commonly used in equipment with moving parts, such as gears and bearings. There are specific grades of lubricants that are suited to different applications. If the grade of lubricant used is known, the chemical properties of the lubricant can be tested. Using oil analysis the quality of the lubricant and material constituents can be tested and compared against the original specification. Oil analysis can be used to determine when an oil change out is required, but also can detect wear of internal components. The following gives some examples of where the oil change would supercede change frequency based on run hours:

- high iron content indicating wear and tear (may require further investigation of the equipment)
- breakdown in the oil additives
- high water content
- changes in viscosity levels

For example, if the gears inside a machine are wearing, fragments of metal are deposited in the oil. When the oil is tested, traces of this metal debris shows up and will give the maintenance team prior warning of a potential failure. The type of metal detected also will give useful information as to its origin (i.e., bearing or gears, etc.). The oil samples are generally taken by technicians in-house and then sent to specialist chemical labs for testing, following which the test results will be issued.

Oil Analysis – Practical Applications

Oil analysis programs allow a condition based approach to oil changes rather than a fixed interval or by equipment run hours.

Results obtained from the oil analysis program can identify optimum frequencies for oil changes and also indicate equipment deterioration and overheating. The oil analysis reports are compiled for the equipment sampled using lab results and circulated to the maintenance area owners giving useful information to act on. Refrigeration compressors, air compressors, standby electrical generator engines, and electrical transformers are among common equipment that oil analysis programs can be applied to.

Ultrasonic Measurement

Ultrasonic Measurement Principles

Ultrasonic measurement is primarily used for leak detection on steam and air systems, but it also can be used to detect leaking valves.

Ultrasonic measurement instruments translate high frequency sounds produced by steam or air leaks into the audible range were users hear them through head phones and can view these sounds on a meter or display.[3] The high-frequency ultrasonic components of these sounds are extremely short wave signals that tend to be fairly directional. It is easy to isolate these signals from background plant noises and detect their exact location. Figure 4 shows an ultrasonic measurement device.

Ultrasonic Testing of Steam Traps – Principles

As mentioned at the beginning of this section, ultrasonic measurement is primarily used for checking the operating condition of steam systems traps. Steam traps are used on steam distribution lines to remove unwanted condensate build up. When a steam trap fails, the build up of conden-

Figure 4. Ultrasonic measurement instrument.

Application/Faults Identified	Benefit
Thermal Imaging - 31 faults found in electrical panels	Avoidance of equipment faults occurring/overheating/serious incidents.
Thermal imaging used to survey the insulation of the site steam distribution. Recommendations for insulation repairs and upgrades were issued.	Initial estimates show a potential reduction of the annual cost of steam generation by 3%.
Vibration Analysis - 26 Level 3 faults requiring bearing changes - 25 Level 2 faults requiring belt changes, greasing, or balancing	Level 3 faults are classified as "failure imminent." For GMP systems feeding production an equipment failure could have severe impact. Level 2 faults are classified as "high vibration." This maintenance teams have adequate time to plan for remedial action.
Ultrasonic Inspection - 16 steam traps found failed and were replaced/repaired - Ultrasonic leak inspection program on the site compressed air distribution	Savings identified based on energy losses due to steam leaking to drain. Savings identified on manifolds and valves found to be leaking compressed air.
Oil Analysis - Oil change outs on site are condition based - A number of oil changes were prompted following oil analysis results	Condition based approach to oil change outs and detection of equipment related wear degradation.
Laser Alignment - Alignment of 9 motor/pump arrangements to industry standard	Reduction in seal, bearing wear and energy usage compared with poor alignment.

Table D. 2010 summary of results.

sate can dramatically increase in temperature, due to the live steam mixing with the condensate. This will result in additional demand on site steam boilers, poor efficiency of heating coils, potential for water hammer in the steam pipework, and an overall inefficient steam system. Steam traps are temperature and condensate sensitive devices that open and close automatically to allow condensate build up to be removed to drain or condensate return. Steam traps can fail open (in which case both steam and condensate passes to the drain) and fail closed (which allows an internal build of condensate in the steam line). The fail open steam trap can be detected by the ultrasonic frequencies present from the steam and condensate continuously leaking through the trap. A fail closed trap can be detected by the absence of ultrasonic frequencies at the trap. Steam trap manufacturers provide steam loss Tables (100% Trap leaking steam). When the capacity of the steam system (Kg/hr) and the size of the steam trap are known, the failed percent can be factored in to calculate the real steam loss.

Periodic steam trap surveys using ultrasonic measurement to identify faults can have significant cost savings by increasing the efficiency of the steam system.

Expected Results

This section gives an overview of the 2010 summary of results for a mature PdM program applied to utility systems at a large pharmaceutical/biopharmaceutical plant (90 acre site). Table D – 2010 provides the summary of results.

Summary and Conclusions

This article has presented in detail the emerging area of Predictive Maintenance (PdM) which has many applications for utility systems in the pharmaceutical industry. PdM is a widely accepted approach to the maintenance strategy for both GMP and non-GMP utilities equipment. The benefits of PdM can be seen and it also promotes a proactive approach to maintenance. Any facility with utility systems should employ some methods of PdM. Initial investment is negligible as PdM programs have been shown to pay for themselves many times over through increased plant reliability and a more proactive approach to maintenance.

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Further Reading

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Online Rouge Monitoring: A Science-Based Technology to Measure Rouge Rates

by Nissan Cohen and Allan Perkins

This article presents the implementation and installation of an online rouge monitor which measures in near real-time the rouge rate and rouge accumulation (metal loss) over time helping to determine derouging and passivation frequency based on empirical data.

Introduction

Rouge is a common phenomenon found in pharmaceutical hot water and steam systems. The use of SS 316L, in the pharmaceutical industry waters at or above 65°C, has enhanced the proliferation of rouge contaminated systems. The primary constituents of rouge are various iron oxides and hydroxides; however, rouge also may contain chromium, nickel, and molybdenum oxides. While the discoloration of SS 316L piping, accessories, and vessels due to rouge deposition is not a problem in itself, any contamination of the product from the rouge is a problem.

Numerous strategies have been implemented to derouge and passivate a pharmaceutical water system. Although many QC/QA personnel find the rouge unsightly, there is little understanding of the rouging process, including its migration in the water system, why and how certain areas are affected by rouge deposition and others are not, or the impact on the final product. Current methodologies for determining the frequency of derouging and passivation are non-scientific assessments based on subjective determinations of the QC/QA personnel in the absence of an objective measurement technique. Decisions are made having economic impact without objective data.

Pharmaceutical water systems are 24/7 continuous operations. The introduction of an online rouge monitor with real-time measurements of rouge rate and resultant rouge accumulation can be an invaluable tool to the operation and maintenance of a hot pharmaceutical water system, providing a scientific validation and real-time assessment of derouging and passivation frequencies.

Background

Rouging is a description of corrosion deposits found in stainless steel systems. Rouge can vary in color from a light-red or orange to a dark brick. Dark purple or black colors are normally found in steam systems with varying colors due to hotter temperatures. Most often the light-red composite material of the deposits is primarily iron hydrated oxides. However, components of rouge also can include chromium, nickel, and molybdenum oxides. The following are three identified classes of rouge:[1]

- Class I Rouge – is deposited corrosion product, consisting of iron oxides and hydroxides originating elsewhere in the system and deposited downstream. The underlying stainless steel surface beneath such deposits usually remains unaltered. This rouge deposit can usually be easily wiped away.
- Class II Rouge – is an adherent corrosion product originating

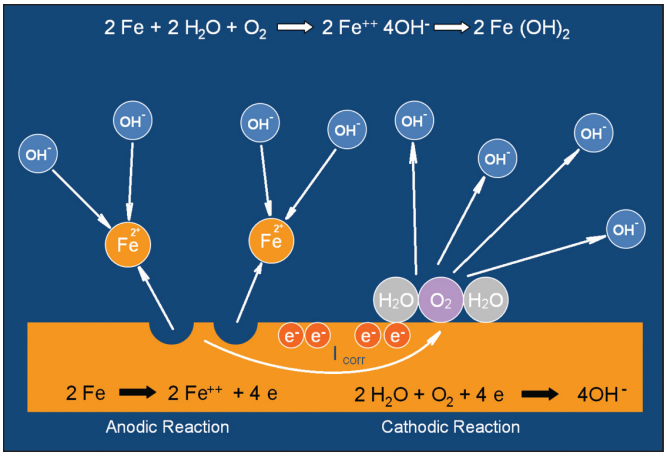

Figure 1. Simple corrosion reaction.

in-situ on unpassivated or improperly passivated stainless steel surfaces. By its formation, the normally passive protective film on the stainless steel surface is altered.

- Class III Rouge – is a blue or black, mostly iron oxide corrosion product, commonly called magnetite, which forms on surfaces in high temperature steam systems. On electropolished surfaces, corrosion deposit may be glossy black, stable, and adherent. On unpassivated mechanically polished surfaces, the corrosion deposit may be powdery black and may slough off.

Non-adherent rouge corrosion products (Class I) may deposit in numerous locations in a high purity water system and are not limited to only stainless steel surfaces. Non-metallic surfaces of Teflon, ETFE, PTFE, and other derivatives seem to attract migrant rouge particulates.[2,3,4] Some non-metallic surfaces have an affinity for rouge deposition, which may be due to physical electrostatic properties.[4]

Rouge is a corrosion product. Corrosion is an electrochemical process. A simple corrosion reaction of iron in water is shown below.

$$2\ Fe + 2\ H_2O + O_2 \rightarrow 2\ Fe^{++} 4OH^{-} \rightarrow 2\ Fe\ (OH)_2$$

Iron in the presence of water and oxygen yields ferrous hydroxide which may subsequently be oxidized to ferric hydroxide. The total corrosion reaction is broken into two components, the anodic and the cathodic parts of the reaction - *Figure 1*. Metal ions from the anode release electrons. These electrons move as the corrosion current (I_{corr}) to the adjacent cathodic areas where a cathodic reaction occurs. Several cathodic reactions can occur, but there is no metal lost from the cathode. If we could measure the electron flow i_{corr}, then we could measure the amount of metal ions going into solution using Faraday's laws and thus the corrosion rate.[5] In reality, we have to measure this current indirectly. This is done by applying a small potential between two electrodes (2ΔE) and measuring the resultant current that flows (i_{meas}) between the two electrodes. As the corrosion rate increases, i_{meas} increases.[5,6]

The relationship between the externally measured current (i_{meas}), the corrosion current (i_{corr}), and the externally applied potential across a single corrosion interface (ΔE) was first derived by Stern and Geary in the January 1957 edition of The Journal of the Electrochemical Society.[7]

$$i_{corr} = \frac{b_a b_c}{2.303(b_a + b_c)} \frac{i_{meas}}{\Delta E} = \frac{b_a b_c}{2.303(b_a + b_c)} \frac{1}{R_p}$$

Where:

b_a = Empirically determined anodic Tafel Slope
b_c = Empirically determined cathodic Tafel Slope
R_p = The Polarization Resistance of the Corrosion Interface

Rouge is corrosion and corrosion rates of metal alloys in water systems, in a wide range of industries, have been successfully measured by standard electrochemical methods for more than 50 years. These water systems include cooling waters, process waters, potable waters, boiler waters, aqueous chemical processes, food processes, and pulp and paper processes. The main differences between these applications and those in the pharmaceutical industry are the low corrosion rates and the low conductivity of the water in the pharmaceutical industry.

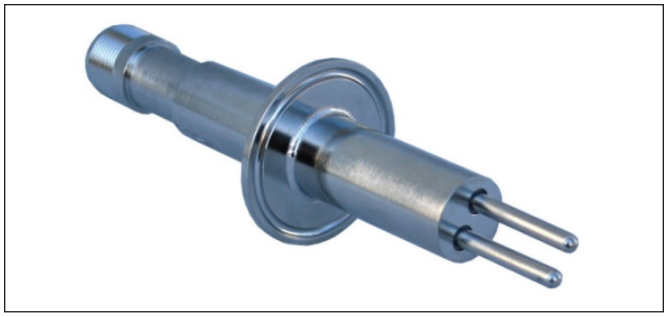

Figure 2. Rouge monitor two electrode probe.

This electrochemical technology, its theory, applications, limitations, and interferences are covered in ASTM G96 – 90(2008) Standard Guide for Online Monitoring of Corrosion in Plant Equipment (Electrical and Electrochemical Methods).[6] The method for computing corrosion rates from electrochemical measurements are covered in ASTM G102 – 89(2010) Standard Practice for Calculation of Corrosion Rates and Related Information from Electrochemical Measurements.[5]

The conversion of the electrochemical currents that are measured at the metal water interface are converted into corrosion rates, as described in the above standards, through constants and empirically determined values, called Tafel slopes. The Tafel values depend on the mechanisms controlling the movement of ions at the metal water interface, such as charge transfer, diffusion control, and transport of metal ions in oxide films. Normally, these Tafel values can be determined empirically. The overall correlation of corrosion rates can be made by comparing the metal loss over time on the measurement electrodes or similar pieces of material. In very low corrosion rates and very low conductivity of high purity waters used in the pharmaceutical industry, Tafel values are difficult to measure. Correlation of corrosion rates and actual metal loss also can be difficult to gauge at levels of a few nanometers per month. Sensitivity of the electronics enhances the measurement, stability, and performance of the instrumentation at very low nanometers/month levels.

Although correlation of measured corrosion rates to actual corrosion rates is difficult in low conductivity, low corrosion rate waters, the Tafel values for any particular set of operating conditions are usually relatively constant. Consequently, a doubling of the measured corrosion rate will correspond to a doubling of the actual corrosion rate. Generally, the change in corrosion rate is much more important than the absolute magnitude of the corrosion rates. The aim of monitoring is to determine the incidences of high and low corrosion rates, and the operating conditions that correspond to each. It is possible to identify and minimize the time for high corrosion

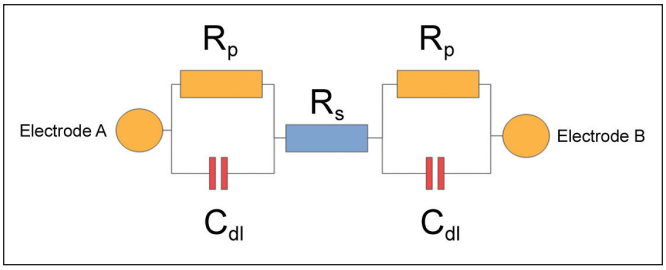

Figure 3. Components of equivalent circuit.

rate conditions, identify these conditions, and maximize the time for low corrosion rate conditions. These conditions can have a major impact on the resultant corrosion rate and metal loss affecting the pharmaceutical water rouging rate.

The ASTM Standard Guide G966 depicts an equivalent electrical circuit that represents the metal/water corroding interface of a typical electrochemical corrosion probe. If the values that are applicable to stainless steel in ultrapure water at 4.65 Megohm-cm water, corroding at 10 nanometers per month, the components of that equivalent circuit are shown in Figure 3.

In this case, Rp would be 1 Megohm, and Rs would be 511Kohms. The value of Cdl might typically be about 100 microfarads. Since the maximum potential that can be applied for theoretical validity of the measurement is about 20 mV between the electrodes, the measured currents are around 8 nanoamps. At a resolution of 1 nanometer/month, this means a resolution of 800 picoamps, which is a very sensitive measurement to make in a field application.

Due to the very small currents to be measured, high input impedances must be maintained to prevent leakage currents. In addition, special measurements are required to determine the value of the solution resistance Rs to subtract from the total resistance in order to determine the required value of Rp. Rp is inversely proportional to corrosion or rouge rate. High rates of rouge, such as 400 nanometers/month, are difficult to measure because Rp becomes very small compared to Rs. Fortunately, it appears that most rouge rates, in pharmaceutical waters, are in the single digits of nanometers/month with excursions typically not higher than a few tens of nanometers per month.

Calibration tests on the rouge monitors used in this study show an accuracy and repeatability of better than 1 nanometer/month has been achieved as measured on the equivalent circuits for rouge rates of 0 to 400 nanometers/month in 4.65 Megohm-cm water. This indicates that a high performance instrument is capable of measuring the low rates of corrosion, or rouging, of stainless steel in ultrapure water. Laboratory and field trials are on-going to further prove the performance and investigate the causes of change in the rouging rate in high purity and ultrapure water.

Industry Wants and Needs

Derouging and repassivation frequencies are based on either time duration or on a visual inspection of the piping or vessels. Since no accurate method or technology has been employed to measure rouge, QA/QC personnel were obligated to use subjective influences to determine derouging and passivation frequencies. Thus, SOPs were developed to derouge and re-passivate based on time duration, i.e., annually, biannually, every six months, every scheduled shutdown, etc., which was based on QA/QC risk comfort levels. Pharmaceutical companies routinely perform preventative measures to ensure compliance to SOPs even if the procedure may not be warranted. Derouging and repassivation may be a prime example of this.

An accurate measurement method for corrosion or rouging rate will help determine the operating limits before derouging and re-passivation are required and offer greater insight into the rouge formation process. Rouge formation is a steady process in all metallic piping systems, but is exacerbated by high temperature and metal composition.[8]

Measuring the rouge rate can help determine the rouge levels of the system and may help determine the probable concentration of rouge in the final product. Changes in the rouge rate may result from operational influences of flow, points of use, pressure, oscillations in water temperatures, and supply or make-up issues.

Modern pharmaceutical water systems are completely automated and computer controlled. Many online instruments have replaced or augmented laboratory testing.[9] Online instruments can be used for real-time release.[10] The integration of an online rouge monitor within the existing network of instruments and computers on the water system is preferable for analysis and correlation with other process data, while adherence to 21 CFR part 11 is maintained.

Derouging and Passivation Economics

Derouging and passivation are different processes, but require similar procedures. Etching chemicals are needed to remove the rouge from the base metal. Once the metal is clean of rouge, the re-passivation of the metal surface can follow. Typically, phosphoric, citric, nitric, and other acids are used for derouging and passivation. Acids are used to remove rouge and passivate, while caustics of NaOH or NH_2OH are used to neutralize the acids before disposal. Disposal is usually via the sewer and drain system, but in certain cases onsite wastewater treatment facilities are used. The rinsing the system of all residues is paramount before the water system can be reactivated for production. Any residual chemicals in the system can and will upset the water chemistry limits.

A typical derouging and passivation shutdown can last from two to seven days depending on how many loops need to be processed and the breadth of the system.

Below are calculations for the derouging and passivation costs of a pharmaceutical water system. This water system has a 20 GPM (76 LPM) USP Purified loop with feed to a 4 GPM (15 LPM) distillation unit, serving a 10 GPM (38 LPM) recirculating WFI hot water loop at 85°C with storage. All piping is 2" (50 mm) and the total piping for all loops combined is 1,000 feet (300 meters).[11]

The derouging and passivation costs for the distillation unit, USP purified, and WFI water loops and storage is $30,000, priced by a derouging/passivation service organization. This includes all chemicals, neutralization, and third-party labor.

Additional costs to be added to the $30,000 figure are downtime of production in days, client's labor, and non-production of products over the shutdown time period. Since each product produced has a different retail and cost value, the final figure can be quite different between manufacturers. A very conservative estimation is a total of $50,000 for all costs. Larger systems with more loops, more expensive downtime calculations, and more expensive products can increase the costs to many hundreds of thousands of dollars per treatment.

The economic issues are calculable, but the overriding consideration is how often is derouging and repassivation currently performed and why? Due to the unavailability of exact rouge rate and accumulation measurements, common assessments are based on either historical trending of other instruments or subjective assessments of coloration. At no time was an assessment performed to determine if rouge had actually been assayed in the final product. The monetary investment in derouging and passivation is high. The delay of an unnecessary derouging and passivation treatment could save tens of thousands to hundreds of thousands of dollars per year per site.

Field Application of the Rouge Monitor

The online rouge monitor comprises front end probe/transmitter, remote display unit, data logger, and analog retransmission unit - *Figure 4*. The analog outputs are connected directly to the DCS, SCADA, BMS, or process control system, while the on-board data logger enables independent data accumulation with direct data transfer to a computer. The display unit provides power and RS 485 digital communication to the sensing probe and transmitter enabling the display unit to be mounted up to 4,000 feet from the probe/transmitter. The unit displays values of rouge rate in nanometers/month or microns/month, and rouge accumulation or metal loss in nanometers or microns.

Corrosion or rouge rates are rarely uniform. Previous studies have shown that some active points for rouge may include pumps and spray balls.[12] Theories abound, but devices such as pump impellers, spray balls, and flow restrictors may have velocity related actions causing erosion of the passive

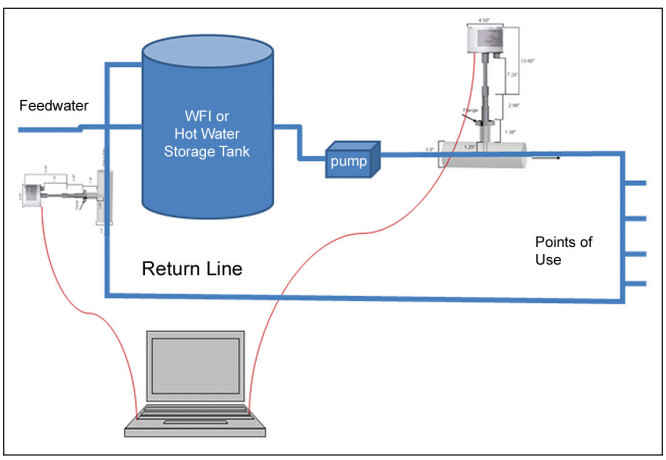

Figure 5. Recommended location of rouge probes in the water system.

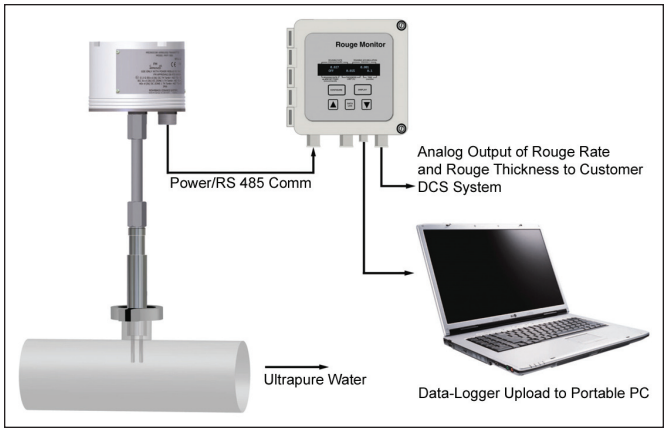

Figure 4. Configuration of the rouge monitor.

layer. Base metal will corrode easily without the passivation layer.

The installation of a rouge monitor closely downstream from the pumps was chosen to pick the higher turbulent areas of the flow where erosion may be greater. Additionally, a second rouge monitor was installed on the return loop before discharge into the WFI storage tank. The rouge monitor configuration and location in the system is shown in Figure 5.

The online rouge monitor was installed on the secondary loop WFI water system that is used for lab testing and small batch production, where water usage is variable. The lower graph in blue denotes the "Rouge Rate." In Figure 6, initially, the new electro-polished SS316L probe electrodes showed a high initial corrosion or rouge rate of more than 50 nanometers per month exponentially decreasing over 24 hours before stabilizing at a low level of 1 to 3 nanometers per month in the WFI water. From there, until 7 February, the rate increased slowly from 1 to 3 nm/month to 3 to 5 nm/month.

Figure 7, expanding the view of data for 6 February to 8 February, shows the values of rouge rate of around 3 to 5 nm/month. Notice, at around 11:00 AM on 8 February, the rouge rate drops precipitously to 1 nm/month and remains at that level for the successive readings. Shortly after 11:00 on 8 February, the points of use were opened for a new fill line. The rouge rate changed due to the operational characteristics of the hot WFI water system. When the water was recirculating,

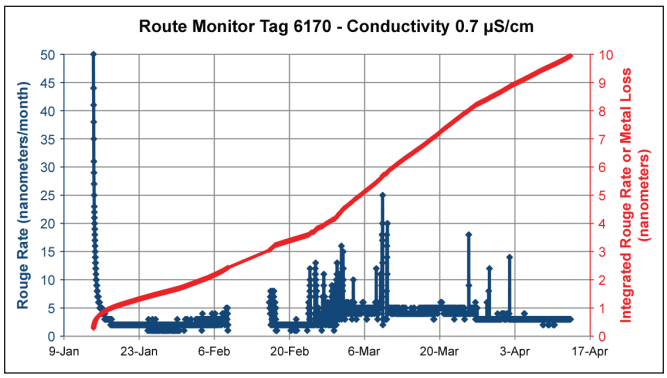

Figure 6. Rouge rate (in blue) and rougeaccumulation over time (in red) in a WFI variable flow filling operation.

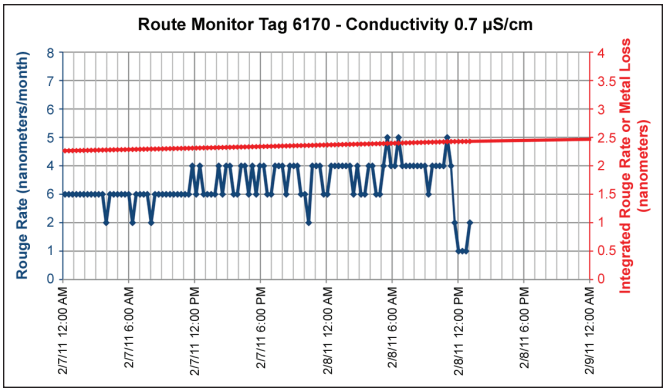

Figure 7. Zoom of data in previous displayed Figure 6.

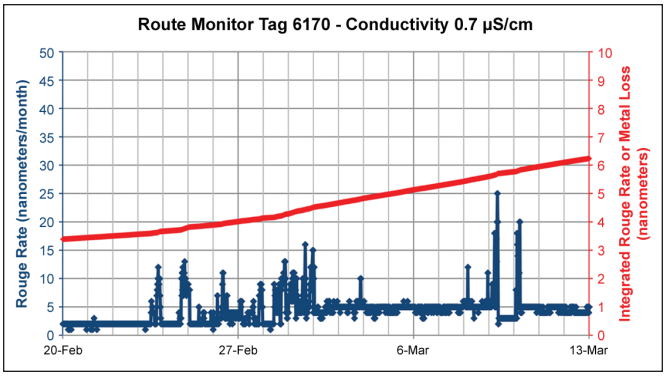

Figure. 8. Detail of graphed excursions of rouge rate between February 20 and March 13.

with minimal usage, the rouge rate built up to a 5 nm/month level. As the use points were opened, the decreased residence time of the water in the recirculating piping system showed a dramatic reduction in rouge rate.

In general, from mid February to mid March there were significant rate fluctuations with occasional excursions up to 20 to 25 nm/month with patterns that are clearly related to process changes. For example, on 9 March there is a sharp increase up to 20 to 25 nm/month in Figure 8 for several readings before settling back to a constant 3 nm/month with additional fluctuations two days later. Similar patterns occurred on 23 February to 27 February and on 27 February to 28 February. The fluctuations are examples of operational changes in the water system due to flow, velocity, use point usage, temperature, and recirculation.

Certain conditions are needed for rouge to develop. There is no science on what these conditions may be, only speculation. Theories abound about rouge development due to the subtle metal composition differences of SS316L, temperature levels, chromium, molybdenum and nickel percentages, carbon dioxide saturation, and other possibilities.[13] There is no proven theory and there is a possibility that some or all of these influences may have a causal affect.[4] The online rouge monitor is a unique instrument providing "Rouge Rate" measurements with accuracy down to single digit nanometer/month levels.

The measurement of very low level rouge rate and metal loss in WFI water systems should not be surprising. The water has been previously treated by advanced purification train components of reverse osmosis, ion exchange, and distillation. These process steps are to remove various impurities in the water. Since the rouge is an end product of corrosion and typified in hot water systems, the source of the rouge is contained in the piping and vessels downstream of the purification train components. The very small and trace amounts of rouge in the water does not appreciably affect the conductivity of the water. Measuring the presence of rouge with conductivity alone is not a discreet detection of rouge in the water as other materials, primarily gases, in the water are contributing to the major conductivity shifts until equilibrium is attained.

The graph data shows extremely minute traces of rouge and very small accumulation over time. The minute concentrations of rouge in the water provide data of the possible concentration of rouge that might be found in the final product. Laboratory analysis would need extremely small detection limits to determine if rouge was found in the final product.

Many previously unanswered questions can be answered with real data and operational characteristics. Example: What accumulation depth or rouge rate is considered acceptable and how is this determined? What is the accumulation over any given time period? When will a rouge accumulation/deposition of X, Y, or Z be accumulated? The rouge rate and rouge accumulation data will help determine the limits before a derouging or passivation treatment is needed. If the current rouge rate is 3 to 5 nm/month and the accumulation is just more than say 20 nm to date, it may still take years before a user-assigned limit is reached to initiate derouging and passivation. If the previous protocol was to derouge and passivate annually and now the treatment can be delayed two or three years, due to the data, what are the savings to water system owner?

Further field experience with the rouge rate data and related process conditions will help define operational practices to avoid breakdown of passivation layers and exposure of base metals. It will allow a better understanding of water chemistry deviations, and velocity erosion effects. Continuous 24/7 operations need real-time measurements to maintain operational consistency within proscribed limits guaranteeing quality products.

Future analysis and a follow-up article will be written to assess the long-term operation of a rouge monitor and investigate changes in rouge rates and metal loss over long periods of operation. These long-term analyses will help define the viability of passivation treatments, passivation durability, derouging frequency, and definitive cost savings for a monitored system.

Conclusions

The use of an online rouge monitor can measure actual rouge rates and metal loss over any time period allowing user-defined limits to be substantiated with empirical data. The determination of derouging and passivation are then based on user-assigned limits and not based on a subjective time period set by the QC/QA Department. The rouge rate may help determine the probable concentration of rouge in the final product. Most significantly, optimization of derouging and passivation treatment frequency could save tens of thousands

to hundreds of thousands of dollars per site annually with scientific data and justification.

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Determining Acceptable Levels of Weld Discoloration on Mechanically Polished and Electropolished Stainless Steel Surfaces

by Ken Kimbrel

This article will identify acceptable levels of weld discoloration on mechanically polished and electropolished stainless steel surfaces and also show proven shop and field remediation practices to removes excessive heat tint. Additionally, we will show the effect of various oxygen levels and the impact heat tint has on corrosion resistance. The information herein is based on actual field experiences and successful methods of field remediation.

Introduction

For years the pharmaceutical industry has relied heavily upon the American Welding Society's AWS D18.2 weld discoloration chart[1] to gage the acceptability of color in the Heat Affected Zone (HAZ) for welds in piping systems. The current ASME-BPE ©2009 edition, Table MJ-3 states in part discoloration in the heat affected zone of product contact surfaces *"may be permitted to have light straw to light blue color" (for example, AWS D18.2 samples 1 through 3 may be used as a guide)."* The AWS D18.2 chart in Figure 10 attempts to offer a guide based on welds made with oxygen contents of 10 to 25,000 PPM and identifying a corresponding sample number and thus identifying not only color, but acceptable oxygen ranges in the backing gas. However, there has been little proof established if color beyond level 3 impacts the corrosion resistance of the weld area or heat affected zone on austenitic stainless steels.

During the inspection process of a piping system, color determination and acceptance of color is at best subjective. Many individuals making acceptance determinations have not been adequately trained to determine the acceptability of color, nor have they undergone an annual visual color acuity test. Without standards giving clear direction on illumination and inspection equipment, many may be using inappropriate or outdated equipment with poor lighting sources which can affect the clarity and representation of the color.

Dr. Lisa Nath, lead eye surgeon at the University of Pittsburgh, contacted regarding the importance of color acuity tests, stated, *"If the ability of these inspectors' job duties depends on the subjective nature of their vision, I would think that an annual exam is warranted."* She further explains, *"Color vision comes about from our possessing three types of cone cells: red sensitive, blue sensitive, and green sensitive. Wavelengths of light are absorbed by these cone cells, and each cone pigment absorbs a broad range of wavelength although each wavelength is not absorbed equally. Our brain, in a very complex way, interprets the wavelengths by mixing excitatory receptive (brain cortex) fields and inhibitory receptive fields and we interpret color.*

Color vision defects can be divided into congenital and acquired. Hereditary color defects are almost always red-green and affect 8% of all males and 0.5% of all females. Acquired defects are more often of the blue-yellow variety and affect males and females equally.

Congenital color vision defects usually are not associated with any noticeable retinal or optic nerve pathology, but acquired color vision defects frequently are associated with observable ocular pathology.

Ideally, a color vision test should detect the presence or absence of normal color vision and also distinguish between red-green defects and blue-yellow defects (remember that blue-yellow defects are primarily acquired color vision losses)."

The ASME-BPE 2009 edition in regard to Inspector/Examiner qualifications states in GR-4.1.3 **"Certification,"** *"The employer is responsible for training, testing, and certification*

"This article will introduce for consideration color samples similar to those shown on the AWS D18.2 chart performed on electropolished 316L stainless steel in an effort to show the need to for an industry accepted color chart for electropolished material."

of employees. The employer shall establish a written practice in accordance with the guidelines of ASNT-SNT-TC-1A including:

a. the requirements listed in Table GR-1
b. training programs
c. certification testing requirements
d. eye exam requirements
e. certification documentation

The owner / user is responsible for verifying the requirements of this section are met."

The SNT-TC-1A is a guideline to be used by employers to develop their own in-house program to cover training, qualification, and certification of their employees performing nondestructive tests.

It is important to point out that the SNT-TC-1A is a guideline and not a mandatory set of rules. It should also be noted that SNT-TC–1A is revised every few years, but, unless otherwise required, there is no requirement that the latest version be adopted. In other words, the SNT-TC-1A can be as broad or as limited as you need it to be.

In many instances, welds in stainless steel have been rejected to err on the side of caution. When this happens, it is typically much easier to cut out a weld and re-weld with the expense being absorbed by contractors rather than discuss the merit of the rejection. This ultimately increases cost to the owner of the system, if not at the time of the re-weld, during the installation process in the form of change orders and overruns, then in future installations by forcing the contractors to increase prices.

This weld discoloration or "heat tint" should not be confused with the naturally occurring, transparent oxide film present on all stainless steel which is largely responsible for the alloys corrosion resistance in aggressive environments. The content of the heat tint layer may vary, but most often is a mixture of chromium and iron oxides, and the heavier the oxide layer, the darker the color appears. Underneath the oxide layer, the base metal is typically depleted in chromium and therefore affects the corrosion resistance of the steel in this area. Unless a uniform passive oxide film is restored, these areas in the welds and HAZ where the heavy oxides have formed are prone to corrosion attack, most often in the form of pitting and crevice corrosion.

Many inspectors, customers, and even manufacturers are under the impression that in order to remove heat tint and restore corrosion resistance, the area affected must be ground to remove metal and passivate or electropolish the area afterwards. This paper will show the effects of these processes and benefits provided.

A high percentage of pharmaceutical systems in service today are fabricated using electropolished 316L stainless steel tubing and fittings. The AWS D18.2 color chart being used for color comparison and acceptance criteria was established on mechanically polished 304L stainless steel. Although the color chart includes a notation *"there was not significant difference in heat tint color from UNS S31603 (steel number 1.4404, Type 316L),"* there is no allowance made for the use of electropolished components in determination of color acceptance and how the increased corrosion resistance benefited the components from the electropolishing process. It is also known that the corrosion resistance of high alloy austenitic stainless steels is usually less affected by weld heat tinting.[2] This article will introduce for consideration color samples similar to those shown on the AWS D18.2 chart performed on electropolished 316L stainless steel in an effort to show the need to for an industry accepted color chart for electropolished material.

As stated in the paper by L.H. Boulton and R.E. Avery, published in April 2004 Stainless Steel World, when defining acceptance criteria for heat tint on stainless steel welds, consideration should be given to post weld cleaning methods that will be carried out on the welds or whether it is deemed that a certain level of heat tinting present on the joints will provide acceptable corrosion resistance in the particular application or environment.[2]

Inspection Equipment

A major impact on the amount of color that can be seen and a problem given very little consideration is the way the weld is being viewed during inspection. Color can vary whether being viewed by the naked eye under room lighting or LED lighting, or by using electronic devices such as a borocope. Dependent upon the type of lamp being used to the type of scope the image is viewed on may impact the "acceptance of color" on a weld.

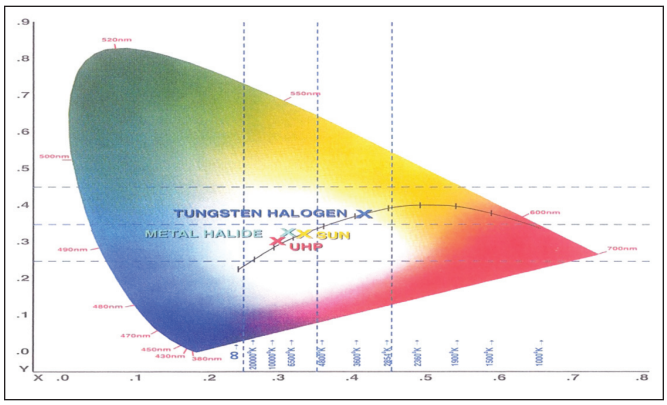


Figure 1. Spectral Output Chart Kelvin vs. Wave Length.

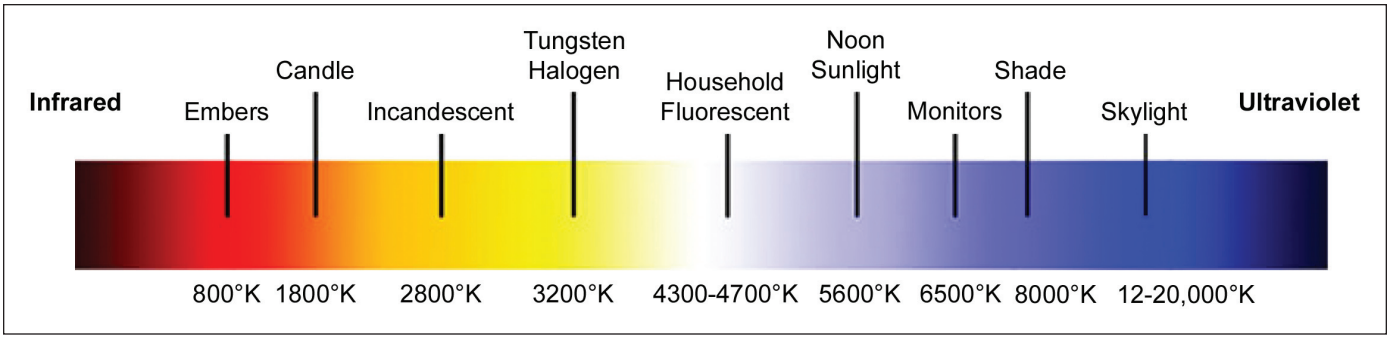


Figure 2. Color temperature imaging.

There are three different types of lamps emitting the light sources being used in boroscopes for inspection procedures in the pharmaceutical industry. These are UHP, which will emit a blue hue, tungsten, which will emit a yellow hue, and metal-halide, which will emit a blue/green hue on the surface. The following chart shows a color hue curve base on the actual light source being used.

Spectral Output

The spectral output of a lamp details the amount of electromagnetic radiation produced across a range of wavelengths, from ultra-violet (UV), through the visible spectrum, to infra-red (IR) - *Figure 1*. Radiation wavelengths are expressed in nanometers (nm), one nanometer being 10–9 meters.

The visible spectrum is between approximately 390 and 770 nm, with ultra-violet being below and infra-red being above this range. In order to give true color images, the light source should have a relatively even output across the visible spectrum. Ideally, the amount of IR radiation produced should be minimized, as IR radiation is converted to heat, which may then require a dissipation system. The spectral outputs of the three most frequently used lamp types are shown in Figure 1 and compared with that of the sun.

Color Temperature

The color temperature of a lamp is an indication of its radiance and is measured in degrees absolute (°K in SI units) - *Figure 2*. Typically, tungsten-halogen lamps have a color temperature of 3,200°K, while metal-halide and UHP arc lamps are around 5,600°K. The color temperature of the sun is 5,900°K. With tungsten-halogen lamps, the color temperature can be reduced by decreasing the voltage across the lamp filament. Some light sources use this method to adjust the "intensity" of the light output. Unfortunately, this "rheostat" type control increases the "yellowing" of the resultant illumination.

According to boroscope manufacturers contacted during the research of this paper, the metal halide is considered to be the closest to sunlight available. An interesting side note is most boroscopes being used in industry are found in the aerospace sector with little consideration being given to pharmaceutical applications where color may be more of a concern.

To further illustrate the effect the light source can have on color, Figures 3, 4, and 5 show the impact of viewing color on welds at different oxygen levels. Each photo in the following three examples show autogenous weld on the outside diameter of a piece of 1-1/2" 316L stainless steel tube split in half. Each

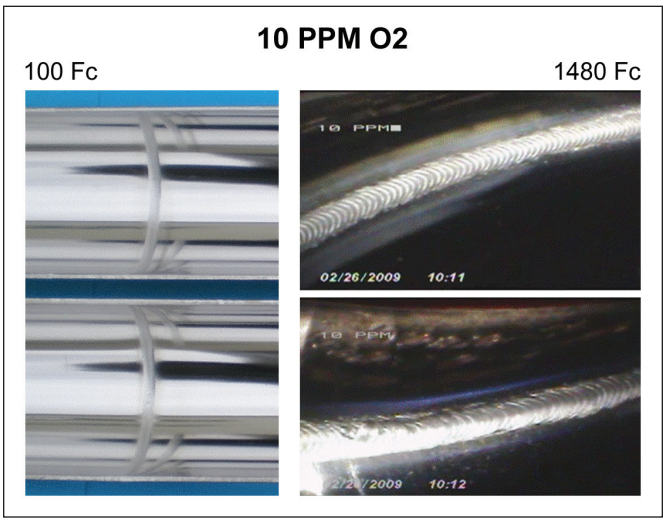


Figure 3. The photo at left illustrates the color on the weld and in the HAZ of a weld made with 10 ppm O_2. The photos far left show the weld discoloration using the naked eye while the photos nearest show the same weld as viewed with a boroscope at 1480 Fc power.

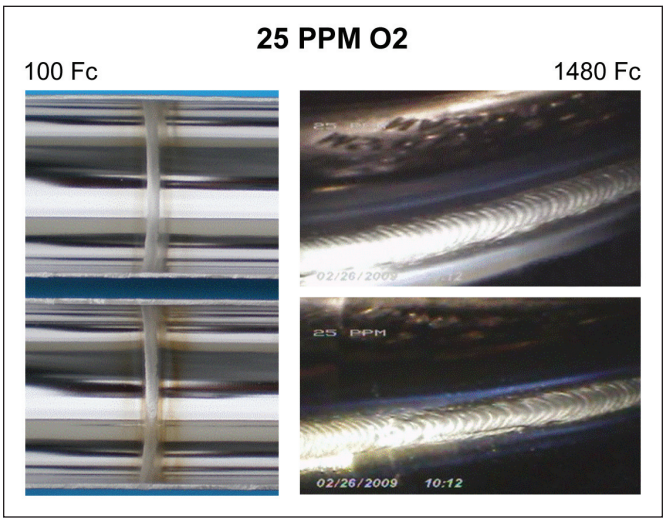


Figure 4. The photo at left illustrates the color on the weld and in the HAZ of a weld made with 25 ppm O_2. The photos far left show the weld discoloration using the naked eye while the photos nearest show the same weld as viewed with a boroscope at 1480 Fc power.

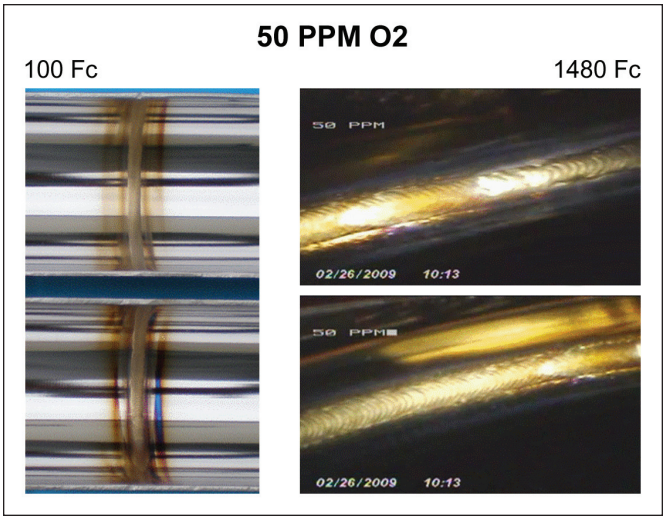


Figure 5. The photo at left illustrates the color on the weld and in the HAZ of a weld made with 50 ppm O_2. The photos far left show the weld discoloration using the naked eye while the photos nearest show the same weld as viewed with a boroscope at 1480 Fc power.

is then examined using the naked eye vs. 1480 Foot candle (Fc) power under a boroscope utilizing a 50W metal-halide lamp.

The identification of weld color is not new to the biopharmaceutical industry and should continue to be identified as a potential problem when necessary. However, with the acceptance of color being fairly subjective, it is important to make sure those responsible for the determination are as well equipped and trained as possible, not only in the determination, but methods for repair. In the following case study, I will illustrate how the difference of opinions can impact a project though both financial and scheduling issues.

Case

In February 2009, a major US-based pharmaceutical company installing new piping and transfer panels contacted the fabricator of the panels indicating over thirty welds were rejected by the third party inspection company based on unacceptable color in the HAZ of the welds as illustrated on the AWS D18.2 color chart. The panels themselves had been inspected and accepted in the fabricators facility nearly two years earlier by a different inspector employed by the same inspection company and had been kept in storage up until this point of installation. The current third-party inspector on site had not only rejected the welds based upon his determination of color, but also had indicated to the owner the weld must be cut out and replaced. After several discussions with the owner, third-party inspection, and hired consultants, it was agreed there was the possibility of using alternative methods to remove the questionable color and maintain the corrosion resistance in the weld area without cutting out the welds and re-welding in new sections.

In considering alternatives, there were several factors discussed. If the welds were cut out and replaced, spools would have to be fabricated incorporating additional welds over those cut out due to shortening of the section and the new spools being welded in. Several weeks would be added to the project to allow time to cut out the existing welds, fabricate, and weld in the new spool pieces. The introduction of several new welds over the amount of existing welds and the purging challenges of the piping runs offered the opportunity for additional problems to occur. In addition, accessibility to the welds in question were challenging in many cases.

Consultants hired by the third party inspection company insisted that in order to achieve optimum corrosion resistance, if the current welds were to be left in place, they must be ground out and the area passivated or electropolished afterwards. This in itself is an impossible task when dealing with field welds as there is no way to access the area for grinding. Another method considered in lieu of cutting and rewelding the sections was a process known as ElectroChemical Cleaning or (ECC). This was developed as an alternative to using standard passivation procedures for cleaning rouge and other surface stains and had been successful in removing heat tint from heat affected zones in welds in past cases. It was argued the electrochemical cleaning process could achieve the same or improved results by removal of metal by the amount of time and current actually applied to the surface while exposed to electrolyte and achieves a passive surface equal to or exceeding standard passivation practices while not damaging the surrounding electropolished finish.

It was determined by the group that a range of sample pieces would be made on 316L stainless steel tubing with

	Coupon #00	**Coupon #01**	**Coupon #02**	**Coupon #03**
	Clean ELECTROPOLISHTUBE with no weld	~ 20 ppm O_2	~ 50 ppm O_2	~80 ppm O_2
Coupon Set "A"	**A-00**	**A-01**	**A-02**	
Coupon Set "B"	**B-00**	**B-01**	**B-02**	
Coupon Set "D"		**D-01**	**D-02**	
Coupon Set "E", No ELECTROPOLISH-Citric Acid Passivated		**E-01**	**E-02**	E-03
Coupon Set "F", Mech. Pol. and EP		**F-01**	**F-02**	

Coupon #00 Set "A" and "B" were clean 316L factory supplied electropolished tube which was tested to determine the CPP of the material only to establish a baseline for corrosion resistance of the base metal for comparison of corrosion resistance in the weld and heat affected zones of the other samples after the cleaning process.

Coupon #01 Sets "A", "B", "D", "E", and "F" were coupons with circumferential welds welded with 20 ppm oxygen and inspected to color equal to #2 as found on the AWS D18.2 color chart.

Coupon #02 Sets "A", "B", "D", "E", and "F" were coupons with circumferential welds welded with 50 ppm oxygen and inspected to color equal to #3 as found on the AWS D18.2 color chart.

Coupon #03 Set "E" was coupons with circumferential welds welded with 80 ppm oxygen and inspected to color between #3 and #4 as found on the AWS D18.2 color.

Table A. Thirteen sample coupons with representative color in the HAZ of the welds.

Figure 6. Coupon Set A-01.

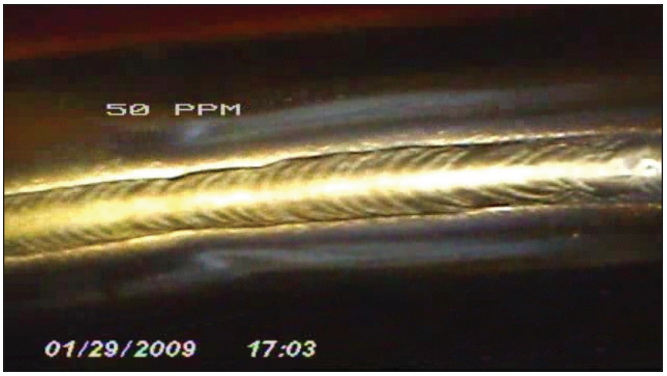


Figure 7. Coupon Set E-03.

the same color discrepancies on the surface. These samples would then be exposed to different methods of remediation, (i.e., electrochemical cleaning, mechanically polished and cleaned), in an effort to determine if in fact the color in question could be removed and if there was an impact on corrosion resistance.

Samples

Thirteen sample coupons with representative color in the HAZ of the welds were provided as indicated in Table A. A modified ASTM G 61 cyclic polarization test to determine the critical pitting potential (CPP) of type 316L stainless steel was used to evaluate each sample after a specific process as listed below. The test solution consisted of 1000 ppm chloride mixed from NaCl with an adjusted pH of 5.0. The CPP is defined as the potential where the current density reaches a level 100 microamps/cm2. The photographs seen in Figures 6, 7, and 8 are representative samples of those shown in Table A and tested with the results in Figure 9.

The Figure 9 graph is a sample shown for reference of the Cyclic Polarization Measurements as charted in Table B. Table B is a summary showing the resulting value of the Critical Pitting Potential as determined by the Cyclic Polarization tests for the 13 control samples. The higher the pitting potential number, the better the corrosion resistance.

Evaluation

In order to evaluate the findings shown in the Cyclic Polarization Results Table, a typical 2B mill finished passive 316L stainless steel will have a CPP near the mid 400 mV level which is an adequate surface for typical corrosion resistance. To further demonstrate the validity of the claim above, a recent study on the evaluation of passive surfaces by Dr. Jim Fritz looked at samples of 316L stainless steel and evaluated the passive surfaces using the Koslow Passivation Tester #2026.[3] The samples had a sulfur range of 0.005-0.017% and had a full penetration weld with color levels between 2-3 on the D18.2 weld color chart. These samples were provided as (1) welded, no post weld cleaning, (2) color cleaned, heat tint removed using Scotch-Bright™ pad (3) ground to 120 grit finish. All samples were then passivated on 9.5% nitric acid at 55°C for 30 minutes. Those results are shown in Table C and Table D.

Review of Color Charts

For comparison of color being viewed through a borocope in a field application and the AWS D18.2 chart shown in Figure 10 being used to establish acceptable color levels, it is important to point out the chart is being viewed on a cut piece of tubing with an unknown light source being emitted on the surface using the naked eye. In most field applications, the welds are being viewed utilizing a boroscope with an unspecified light source or viewing monitor which can emit variations on the outcome as described in the "Inspection Equipment" section above.

Additionally, the findings above suggest that even with color on the welds, the passive surface in relation to mechanically polished material vs. electropolished material is impacted to different degrees. The studies clearly show even with higher

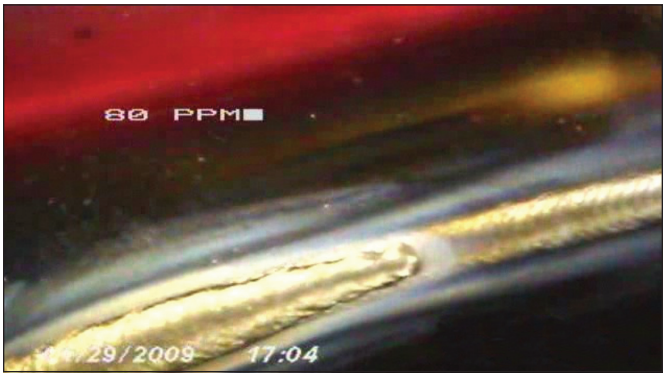


Figure 8. Coupon Set A-01.

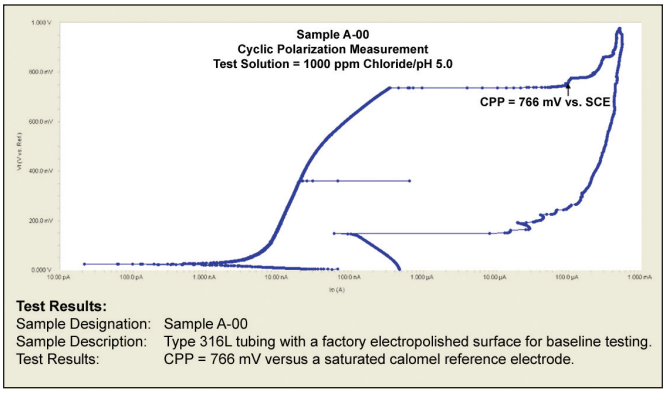


Figure 9. Cyclic polarization measurements.

Sample ID	Sample Description	Critical Pitting Potential (mV vs. SCE)
A-00	Baseline sample – Factory Electropolish	766
A-01	Welded with 20 ppm O_2 – ELECTROPOLISH for 5 min.	728
A-02	Welded with 50 ppm O_2 – ELECTROPOLISH for 5 min.	455
B-00	Baseline sample – Factory Electropolish	764
B-01	Welded with 20 ppm O_2 – ELECTROPOLISH for 7 min.	699
B-02	Welded with 50 ppm O_2 – ELECTROPOLISH for 7 min.	459
D-01	As-welded with 20 ppm O_2	453
D-02	As-welded with 50 ppm O_2	242
E-01	Welded (20 ppm O_2) – citric acid passivation	841
E-02	Welded (50 ppm O_2) – citric acid passivation	451
E-03	Welded (80 ppm O_2) – citric acid passivation	385
F-01	Welded (20 ppm O_2) – Mech. Polished + Electropolish	310
F-02	Welded (50 ppm O_2) – Mech. Polished + Electropolish	423

Table B. Type 316L tube samples – cyclic polarization results.

Sample	Unpassivated	Passivated
As Welded (HAZ)	- 780 mV	- 215 mV
Color Cleaned (HAZ)	- 450 mV	- 322 mV
Ground (HAZ)	- 220 mV	- 298 mV
Base Metal (2B Finish)	- 221 mV	- 258 mV
0 to -400 mV = Passive, -400 to -500 mV = Indeterminate, -500 to -1100 mV = Unpassivated		

Table C. Summary of Koslow passivation test.

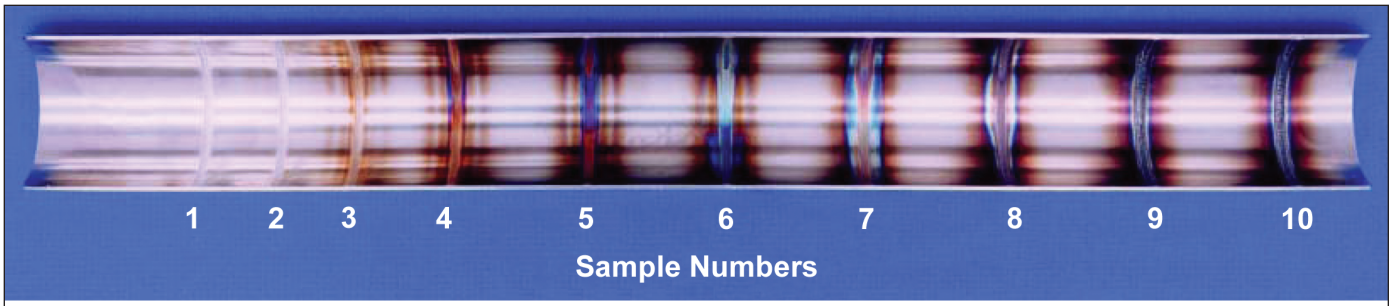
Sample	Unpassivated	Passivated
As Welded (HAZ)	276 mV	525 mV
Color Cleaned (HAZ)	230 mV	475 mV
Ground (HAZ)	343 mV	495 mV
Base Metal (2B Finish)	506 mV	494 mV
Weld		603 mV

Table D. Summary of CPP measurements.

levels of color present, that the electropolished surfaces are more corrosion resistance than those receiving only a mechanical polish. Therefore, color levels on electropolished surfaces may vary from those shown in the industry accepted AWS-D18.2 chart. Figure 10 (AWS D18.2) shows the different colors associated with O_2 levels on mechanically polished tubing in comparison with Figure 11 (Cotter Bros. Chart #143) illustrating color levels typically found on electropolished tubing with similar O_2 levels.

Conclusion

The corrosion testing presented above suggest even with color in the heat affected zones, enhancements such as passivation, electrochemical cleaning, or electropolishing when performed



Notes:

1. The tube sample was prepared by making ten autogenous welds on the outside diameter of a 2 in. (50.8 mm) 316L stainless steel tube. Welds on 304L tubing showed no significant difference in heat tint from 316L. The welds were full penetration welds. The torch shielding gas was 95% argon, 5% hydrogen [99,998 with <2 parts per million (ppm) of oxygen, moisture, and hydrocarbons] to assure full penetration welds. The hydrogen addition to the torch shielding gas is considered to have no effect on the HAZ heat-tint oxide on the inside surface. To provide varying amounts of oxygen in the backing gas a compressed cylinder of medical grade air was added to 99.98% minimum pure argon (<2 ppm of oxygen, moisture, and hydrocarbons) and the oxygen was measured with a calibrated commercial oxygen indicator. The amount of oxygen in ppm in the backing gas was measured to be as follows:

No. 1–10	No. 3–50	No. 5–200	No. 7–1000	No. 9–12500
No. 2–25	No. 4–100	No. 6–500	No. 8–5000	No. 10–25000

2. The illustration should be used as a reference to identify the degree of heat-tint oxide by number and not to specify oxygen limits in the backing gas. The acceptable degree of heat tint can vary with different service environments. It should be considered along with the economics involved obtaining very low levels of heat tint when specifying acceptable heat tint level welds.

   The amount and visual appearance of heat-tint oxide can be influenced by factors other than oxygen, such as:

   - High levels of moisture in the backing gas will increase the degree of heat-tint.
   - Contaminates such as hydrocarbons, moisture, and some types of particulate on the surface prior to welding can influence heat-tint oxide levels.
   - Hydrogen gas in the argon backing gas can significantly reduce the amount of heat-tint oxide.
   - The metal surface finish can have a varying affect on the visual appearance of heat tint.

Figure 10. AWS D18.2 weld discoloration chart.

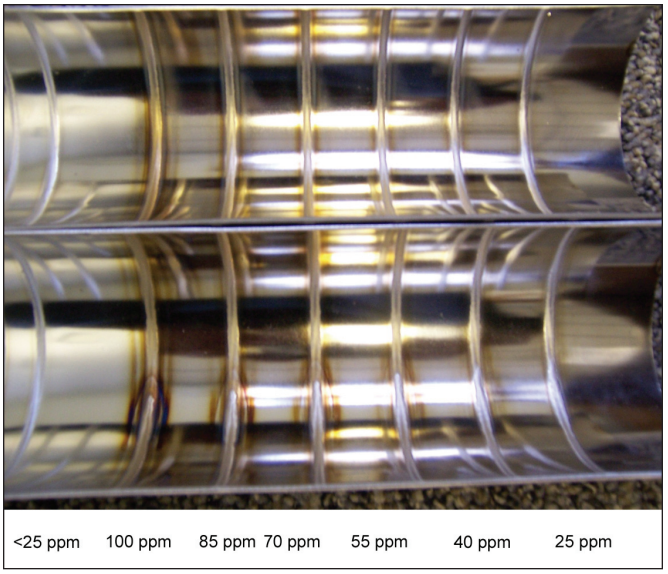


Figure 11. Cotter Bros. chart #143 weld discoloration chart for electropolished material.

properly will further improve the corrosion resistance in that area of concern.

The passivation process may not completely remove color from the HAZ but will improve the corrosion resistance to acceptable levels. Electrochemical cleaning and electropolishing will not only remove the color from the welds and HAZ, but also improve corrosion resistance to acceptable ranges without requiring welds be ground to remove metal and without further passivation processes.

Furthermore, the information above indicates that any resultant weld discoloration up to and including an O_2 exposure of 50 ppm will have no effect on the corrosion resistance recognized in the biopharmaceutical industry for electropolished 316L Stainless Steel material.

It is an inherent problem that inadequate purging of field welds have resulted in residual heat tint formed on stainless steel which may affect the corrosion resistance of the material. To compound this problem, the evaluation of color in the HAZ of welds is subjective at best, and may or may not be evaluated by qualified personnel. There is an inadequacy of industry standards for inspection personnel, equipment standardizing on illumination, image magnification and viewing which can result in enhancing or masking color resulting in either increases in weld rejection, or acceptance of inappropriate welds.

Passivation, although effective at improving the corrosion resistance, may not remove color from the weld or heat affected zone. The current acceptable practice to remove weld color is to grind the area to remove metal and passivate or electropolish the affected area, or cut out and replace on site trying to control the color through proper purging techniques. The corrosion studies have shown, that on-site electropolishing or electrochemical cleaning can effectively remove material and heat tint from the welds and HAZ while improving the corrosion resistance to levels similar to that of the base metal without grinding or mechanical polishing being performed.

A color chart recognizing the effects of color for electropolished material should be developed and adopted for the pharmaceutical industry showing accurate acceptable levels of color - *Figure 11*. Inspectors and those responsible for evaluating color on welds should undergo color visual acuity tests yearly and should provide documentation of testing as deemed necessary by the owner or equipment supplier prior to the inspection process.

References

1. AWS D18.2 Weld Discoloraton Chart.

2. Boulton, L.H., and Avery, R.E., "Heat Tinted Stainless Steel Welds – Guidelines for Acceptance," *Stainless Steel World*, April 2004.

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Engineering and Design Considerations for Thermal Inactivation of Bio-Hazardous Waste Streams

by Juha Mattila

This article presents important considerations when designing thermal inactivation systems for bio-hazardous applications, and provides a comparison between properties of batch and continuous decontamination systems.

Introduction

Downstream processing areas of pharmaceutical production facilities, research laboratories, and bio-containment laboratories are not often highlighted when looking at process solutions. This is often because this equipment is not in any contact with pharmaceutical products or visible in the research laboratory environment. Hidden among other utility-considered equipment, the effluent decontamination process equipment is a very important part of the facility activities required for daily operation and maintaining environmental safety. As environmental safety becomes more and more critical, it is extremely important to have a safe and economical means of treating process waste streams. Awareness of such systems design, purpose of use, requirements, and restrictions is important for upstream processes as well. It is important that architects, designers, engineers, and users take into consideration the designs of facility waste processing as part of the overall facility.

Figure 1. Continuous system.

Applications

Process areas that implement decontamination of bio-hazardous liquid and solid waste include bio-containment facilities, such as biotechnology research laboratories, infection control centers, animal and human pathology laboratories, military research, infection hospitals, university research laboratories, medical research facilities, pharmaceutical production plants, and even food processing plants.

Effluent streams can be sterilized by chemical or thermal means prior to discharge. The process can be a batch process or continuous process. Sterilization is a defined, validated process to inactivate all viable micro-organisms from the effluent prior to discharge. This renders the effluent safe to discharge to a sanitary sewer system. For effluent decontamination, validation may not be a correct term, but when used generally refers to a qualified process performance by microbial challenge testing.

There are two primary means to handle contaminated waste: 1. a batch process or 2. a continuous process. A thermal batch process consists of phases that include receiving effluent to a holding vessel, heating up to and holding at a specific exposure temperature in a decontamination vessel, and followed by cooling sequence, sampling phase, and discharge to drain after verified sample analysis results. A thermal continuous process configuration is a flow-through system that consists of a series of heating and cooling exchangers and a dedicated section for exposure at the specified temperature for a specific period

of time. A continuous process can be sampled directly from the outflow or using parametric approach, as per described below in "Equipment Qualification."

Disinfection usually refers to a chemical process, generally recommended for small scale applications. Chemicals often used include sodium hypochlorite and peracetic acid, due to the broad-spectrum antimicrobial activity. The chemical is added and mixed at a known concentration directly into the effluent batch at a specific ratio, heated if required for more affect, and held for a specific retention time. The efficacy of chemical disinfection also can be verified by direct sampling and microbiological analysis.

The batch-based processes are usually referred to as conventional processes, such as kill tank systems. However, due to the waste-control demands of process and bio-containment facilities, continuous waste-reprocessing systems are becoming more suitable. The effectiveness and added safety of continuous processes have added value to the effluent waste process in modern facilities - *Figure 1 and Figure 2*.

Batch Decontamination System

Basic operation of a batch decontamination system (kill tank) includes the following operational phases:

- receiving/filling
- heating
- decontamination
- cooling
- release/drainage or holding before release

Effluent is either pumped or gravity drained to a collecting vessel. When the vessel is full, the decontamination process can begin by heating up the vessel content by either direct steam injection, heating coils, or jacket heating. If effluent treatment is to be non-interrupting, at least two vessels or more are needed to enable continuous effluent collection ability, depending on the facility daily output and peak maximum flow. After reaching the decontamination set point, the decontamination sequence is carried out by holding the effluent batch at specified temperature for a specified holding time. Typical decontamination temperatures vary between +121.1°C and +134°C and exposure times between 15 and 60 minutes. Maximum design parameters for a batch vessel are usually similar to a steam sterilizer (3 bar/+143°C). Higher design parameters often lead to a very expensive vessel structure. After decontamination sequence has elapsed, the tank is cooled down and de-pressurized by jacket cooling or cooling coils. In bio-hazardous applications, the decontaminated effluent may have to undergo sampling and analysis prior to release to environment (common drainage system). Analysis results take three to five days to be confirmed; therefore, the batch system may need additional vessel volume for batch holding prior to release.

Figure 2. Batch decontamination system.

Continuous Decontamination System

For continuous decontamination systems, the effluent is collected to a collecting vessel in a similar way to batch systems. The continuous effluent processing system is started based on start and stop levels defined for the tank and measured by level transmitter or level switches. The decontamination process tunes up the process (heating and cooling) in a closed loop before the system goes online. Once the heating up period has elapsed, the process will advance to continuous processing mode, where effluent is taken directly from the collecting vessel and is heated, decontaminated, and cooled in a one way process until the stop level of the collecting vessel is reached. Decontamination takes place in a continuous flow through a dedicated pipe section after heating exchangers. There are temperature sensors in the beginning and at the end of the decontamination section, proving the decontamination exposure time and temperature during exposure time and the flow rate is constant. Continuous systems require significantly shorter exposure time due to high pressure and temperature conditions. Typical continuous decontamination temperatures vary between +150 and +165°C and exposure times between three and 10 seconds, depending on required lethality of the decontamination process. Heating media is plant steam. Increasing the decontamination process temperature decreases exposure time requirement exponentially. This applies to sterilization in general. Therefore, exposure times for continuous decontamination systems are significantly shorter, and usually defined in seconds rather than in minutes. After the decontamination section, the effluent flow is directed through cooling heat exchangers prior to discharge. The decontamination process performance qualification is verified during commissioning and due to the type of process and ideal process measurement conditions (turbulent flow, small momentary processing volume through the decontamination section) the continuous process can rely more on parametric control and replication of qualified process conditions.

Process and Equipment Design

The following criteria directly affect the determination of the applicable type of decontamination equipment:

- bio-safety level of the application by environmental national and local laws, regulations, directives, and guidelines
- daily maximum quantity of effluent/peak volume of effluent vs. available technical space
- composition of effluent
- safety and redundancy requirements
- availability of utilities
- qualification requirements

Bio-safety levels (e.g., BSL1 to 4, CL1 to 4, and BL-1 to 4) define the required level of bio-containment depending on the biological organisms present. Levels 1 and 2 stand for minimal or moderate risks and levels 3 and 4 have high risk of infectious diseases and contamination.

Due to low risk of contamination, level 1 and 2 equipments are typically placed in general utility areas with the ability to use liquid disinfectants in case of a leak situation or to service the decontamination equipment. Access to the control system should be controlled by sufficient password protection and operating level limitations. In case of possible future upgrade from level 2 to level 3, a proper bio-containment room design is recommended for decontamination equipment, as well as considering the type of equipment to fulfill future requirements. In such situations, the design should allow for upgrading the existing system easily without considerable re-work of the space or equipment. In such cases, it is recommended to qualify the selected system according to level 3 during this phase, and ensure that the selected system will meet the required demands of level 3 applications.

For higher containment applications, additional design and safety considerations should be followed. The environment and mechanical space access to equipment at level 3 and especially level 4 containment areas is very limited so automatic and self-diagnostic operation with local and remote control, alarm functions, BMS (BAS) monitoring, and "hand-shake" signals communicating system status upstream are required. Strict control system access protection is also very important. In case of an emergency situation, the user should be able to carefully evaluate the equipment status and carry out all required safety measures from outside prior to entering the equipment room. Room decontamination from outside the space using a gaseous process (such as vaporized hydrogen peroxide) fed through specific wall ports should be arranged as well as using applicable liquid sterilants for decontamination of leaks or spills. Service procedures and systems access must be designed accordingly and take into account the restrictions imposed by protective clothing and equipment access for servicing the equipment. Peripheral devices and precautions may not usually be considered part of the decontamination equipment, but should definitively be included in the design of the entire operation. Equipment qualification sets specific demands for the type of process and equipment within level 3 and 4 applications. These issues are studied in "Equipment Qualification."

Daily maximum effluent quantity is an important factor in thermal sterilization systems. Batch processing of large daily effluent loads requires extensive storage and decontamination volumes as well as large technical spaces, which

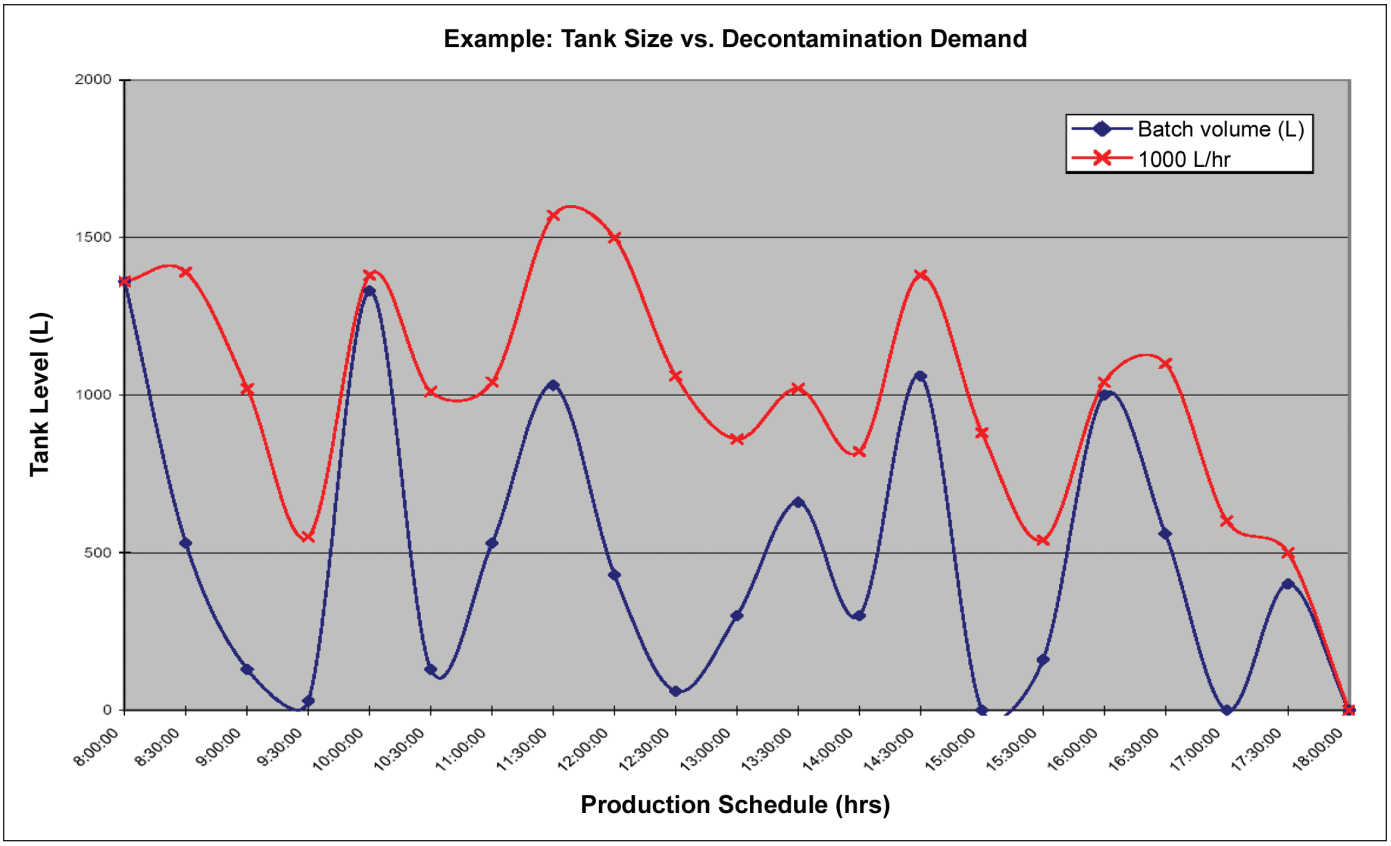

Figure 3. Daily effluent output evaluation example.

is a significant cost factor in new bio-containment facilities. Large batch systems are also often built and tested on site due to being limited by the size of the batch tank skids that can be transported. This makes batch systems more suited for small or single-point laboratory applications with small holding volumes such as table-top or under-counter installations. Continuous sterilization systems require a smaller footprint and can be manufactured and tested outside the facility - *Figure 3*. This makes continuous systems a more applicable solution for large capacities in terms of building and equipment capital costs, operational costs, and qualification.

The capacity vs. unit size efficacy for continuous systems is expanded by increasing only heat exchange surfaces, flow rates, and instrumentation sizes while batch systems require significant increasing of vessel sizes in addition to the need of having higher momentary capacity utility output needs. To be able to continuously receive effluent, it is required to have at least one vessel for collecting effluent and one for batch decontamination. In addition, there may be a requirement for another vessel for batch holding. Sample analysis requires four to five working days leading to equivalent holding time before the batch is permitted to be released to the common drainage system. For continuous systems, sampling can be performed directly from the outflow of decontaminated effluent, but a preferred method is described in "Equipment Qualification."

Table A shows a comparison between a batch and a continuous system. Decontamination capacity is 10,000 liters/day (during 10 hours of operation) for a BSL-3 application.

Stainless steel grade 316/316L is generally acceptable for contact surfaces, as well as PTFE based gasket material for their chemical and heat resistance. Following ASME BPE guidelines for materials of construction, components, and manufacturing methods ensures a reliable and functioning process system, as well as complying with the current GAMP guides even if decontamination systems are actually outside of the GMP (process contact) equipment scope.

For reliable service and consistent cycle results, process components and instruments should withstand steam sterilization and piping design should follow <3d "dead leg" rule where possible. Redundancy for critical process components is important in critical parts of the process (e.g., dual process pumps, dual barrier valves, dual critical temperature sensors, electrical heating for vent filtering, or dual vent filters). A single pass process minimizes any risk of cross-contamination between the contaminated effluent and decontaminated effluent. The design should avoid any return-loop connections between the effluent receiving area and the discharge area. Any shaft seals connecting to the contaminated side, such as pumps and tank agitators, should be avoided. Magnetic coupling is a leak-free solution for such applications. Temperature sensors are subject to frequent calibration and therefore should be installed in welded pockets that are not in contact with effluent. The number of connections should be minimized by applying preferably orbital welding techniques where technically possible, taking into consideration the service requirements of the components. The need for service is also reduced by minimizing the number of components and any moving or rotating parts. Mechanically polished or electropolished finishes for contact surfaces promotes sterilization efficacy and minimizes possible fouling.

Capacity: 10 L^3 / 10 hrs	Continuous*	Batch**
Floor Space Requirement Est. (m^2)	15	68
Steam Utility Size (kW)	77	355
Cooling Utility Size (kW)	53	163
Equipment Heat Loss to Environment (kWh)	18	88
Heating Energy Consumed (kWh)	790	1430
Cooling Energy Consumed (kWh)	530	815
Steam Consumption (kg) (Direct Steam System)	---	2356
*Continuous system with 1000 l/hr operation and 2000 L collecting tank **Batch system with receiving, sterilization and storage tanks		

Table A. Utility comparison table, calculation example.

The effluent composition should be determined during the early stages of the process evaluation to accommodate design considerations for any chemical burden and prepare for possible handling of solids. High chlorine content combined with high processing temperature may require reinforcing process materials, but it is significantly less costly to limit chlorine content to a minimum and dilute in case of higher content.

Regardless of the processing method – batch or continuous – solid particles should be removed from the effluent stream and sterilized separately; even smaller particles than 10 mm in diameter. Larger particles such as carcass parts are usually sterilized and disposed of by using specific alkaline hydrolysis-based tissue digesting systems or incinerators. Solids can include any solid or slurry process residue such as carcass and tissue remains, proteins, agars, coagulated media (blood etc.), animal cage residues (bedding residue, food remains, feces, hair) among others. Direct steam injec-

Figure 4. Solid waste sterilization test load.

tion sterilization in a relatively small volume breaks down solid mass and penetrates through the material, leading to a reliable sterilization result. The batch temperatures must be correctly measured from the coldest points and from the solids load to ensure a consistent result. Therefore, a smaller batch is preferred for solids sterilization.

Slurry and solid containing effluent leads to severe fouling of process surfaces and non-homogenous effluent batches can compromise process qualification integrity. Constant need for Clean-In-Place (CIP) of processing units is expensive and time-consuming, reducing the system uptime. Chemical pre-treatment of solids (e.g., proteins dissolution by alkaline or other) can be a very effective method to prevent fouling, especially for applications with egg proteins (vaccine manufacturing). If needed, correct pH level (7 to 9) should be adjusted for the effluent discharge prior to release to common drainage systems.

In addition to solids removal and alkaline dissolution of proteins, other fouling prevention methods include prevention of steam flashing during the sterilization process (superheated liquid processing), proper air removal, continuous mixing of slurry effluent in a collecting vessel, and keeping all process surfaces wetted at all times. Preventive actions such as adding water for dilution of effluent is recommended, but does not remove the need for the features mentioned above - *Figure 4 and Figure 5*.

Consistent availability of utilities is a common concern in any processing system. Thermal inactivation equipment requires house plant steam and/or an electrically heated system for thermal treatment of effluent, cooling water (closed loop or other type) for cooling down effluent prior to discharge, instrument air for pneumatic actuating instruments, and electricity for powering process components and the control system.

Batch processing equipment requires lower steam supply pressure (3 to 4 bar). The batch process temperatures are typically standard steam sterilizer cycle temperatures (+121.1 to +134°C), but apply long exposure times. Continuous systems require higher steam pressure (5 to 7 bar) for higher decontamination exposure temperatures (+130 to +165°C) and respectively apply short exposure times, from seconds to a maximum of a few minutes. The general theory of exponential time/temperature correlation in moist heat sterilization processes defines the equivalency. Equal or higher kill efficiency when shortening exposure time is achieved by raising exposure temperature respectively. For example, 1.16 seconds at +150°C is equal to 15 minutes at +121.1°C.

Figure 5. After solid waste steam sterilization.

Momentary consumption of steam, electricity, and cooling water of continuous systems is significantly lower to batch systems due to the use of ideal turbulent processing conditions, a superheated liquid process with relatively small amounts of continuous liquid treatment, and an effective heat recovery process. Batch systems also may require direct steam injection, which is not economical in larger applications due to the loss of plant water, residual condensate heating energy, and water treatment chemicals. This can be neglected in small point-of-use applications, but significantly raises annual operating costs in larger systems.

Cooling water and heating steam/electricity consumption can be significantly reduced by applying heat recovery to the continuous decontamination process. This means energy transfer from decontaminated hot effluent to the incoming contaminated cooler effluent prior to discharge. Specific attention should be given to the method of heat transfer. In a single pass solution with contaminated effluent on one side and decontaminated discharge effluent on the other, there is a severe risk of an undetectable cross-contamination. Heat transfer should be arranged so that the effluent streams are separated and pressure controlled where the decontaminated stream is always at higher pressure compared to the contaminated effluent. This reduces the heat transfer efficiency, but bio-safety measures are considered more important to energy savings when operational risks are analyzed.

Safety and redundancy evaluation by hazard analysis and process reliability and efficacy verification by process qualification also define the required characteristics when evaluating the decontamination system and equipment.

Hazards Analysis

Hazards and risks analysis for decontamination systems should be carried out including the related systems, location, and surrounding environment. Minimizing the potential risks coming from the upstream process, laboratory, or other bio-containment activities should be taken into account before selecting the method of decontamination.

Minimize the quantity of effluent being discharged for decontamination. The less effluent produced, the easier the system is to design in terms of safety measures. Leave any unnecessary sources of liquid effluent outside the barrier. Leave out any unnecessary amounts of solids – anything that is harder to handle inside the barrier than outside, for example toilet waste. The more effluent produced, the more holding volume is required. Smaller volumes require smaller equipment and less room space. The smaller effluent stream also reduces the volume that could potentially leak. If a leak does occur, smaller spaces are easier to contain, clean, and decontaminate. High levels of solids can cause excessive foul-

ing, operational problems, and critical downtime unless the decontamination process is designed properly to handle this type of waste.

Minimize the number of connections within the decontamination system – every connection is subject to leakage. Non-visible welds inside any structure should not be allowed in contact with the effluent. In case of a leak, detection in these areas is extremely hard or sometimes impossible. Pay attention to the type of instrumentation, process components, and installation as described below.

Continuous monitoring, self-diagnostics, full coverage alarming system, and repeatable qualification methodology are mandatory features for critical equipment. The end user must be able to safely control the process from outside, and even more important, to be aware of the system status at all times.

Equipment Qualification

Equipment qualification methods and procedures should be required for any effluent processing system within bio-safety level 3 and 4 classified areas. Equipment qualification is based on sampling and laboratory analysis of the decontaminated batch before releasing the batch for discharge to the sewage system. The equipment performance can be qualified by using biological indicators with a specific population of a challenge micro-organism, typically Geobacillus Stearothermophilus. Depending on the bio-safety level of the application, a passing overkill result with a starting population of 106 CFU is generally required, and three consecutive successful tests are considered passing the biological challenge test.

Qualification of a batch process is simple and straight forward, but sampling from large volume vessels can create problems that may not be easily solved. This includes defining a valid and representative number of samples of a batch and a consistent qualification method for non-homogenous batches (including solid particles). Even when particle sizes are restricted, it may be difficult to prevent coagulation within the batch vessel. This leads to uncertainty of even temperature distribution due to pockets of large mass caused by solids coagulation or simply large size particles. Control over air pockets that can cause cold spots and temperature deviation during the batch decontamination are also difficult to prove by sensor monitoring or sampling even if no solids were present. Sterilization cycles are often run prior to servicing equipment. Simple processing equipment is an advantage for batch systems in terms of service cycle qualification, but larger scale systems face the same problem when testing the vessel for sterilization integrity.

In case of prions, specific time/temperature controlled batch inactivation cycles and alkaline-based inactivation cycles are applicable, as well as other processing methods that can be verified as compliant.

Service sterilization cycles of different isolated process sections (filters, tanks, strainers, etc.) are normally considered batch cycles and can be tested as such to ensure efficacy. For continuous decontamination systems, qualification of the process should be based on biological challenge tests and sample analysis for equipment qualification purposes. Momentary processing volumes in continuous processes are minimal, homogenous, and with the aid of turbulent flow (for efficacy in temperature control and heat transfer) offer significant advantages when compared to batch processing conditions. Continuous processes sterilize a very small volume at any onetime and this allows redundant instruments to accurately monitor the process following a PAT type qualification scenario. This provides a significant advantage to batch processes that are challenging to monitor. A parametric release of the effluent is possible in continuous systems by ensuring the daily process parameters match those during qualification. Parametric release is a significant advantage over batch systems that may require sampling of each batch prior to discharge.

Conclusion

Specific attention should be given to the design of the most suitable system for an effluent decontamination application. In addition to technical details comparison and overall applicability to the upstream process needs, the evaluation also should include long term lifecycle evaluation and functionality of the system in terms of qualification capabilities, daily operations, and required service activities. Batch processing systems are more suitable for smaller point-of-use and smaller volume applications, whereas continuous systems are more suitable in high containment applications with critical performance assurance and qualification requirements, as well as larger treatment volumes applications. Chemical processes (e.g., alkaline hydrolysis) are mainly used and recommended for carcass/tissue disposal and chemical disinfection methods for small-scale lab point-of-use.

For example, the NIH and CDC guidelines as well as European Union directives provide an excellent platform for definition of required precautions. However, a specific process design guideline for designing effluent decontamination process equipment could be a very useful addition for guidance to a safer environment and operation.

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About the Author

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Survey of Pharmaceutical Water System Users on the Use of Non-Distillation Systems for the Production of WFI

by Dr. Anthony Bevilacqua and Dr. Teri C. Soli

This article presents the results of a jointly sponsored USP/ISPE survey of the pharmaceutical industry and analyzes the potential to use alternative methods of production (other than distillation) as the final purification in the preparation of Water for Injection (WFI).

Summary

A jointly sponsored USP/ISPE survey of the pharmaceutical industry is presented and analyzed on the topic of the potential to use alternative methods of production (other than distillation) as the final purification process in the preparation of Water for Injection (WFI). The survey was prepared by USP Expert Committee members. It was reviewed, supported, and administered by the ISPE Critical Utilities Community of Practice (CU COP) leadership to the CU COP, and the results were collected and analyzed. The purpose of the survey was not only to acquire data related to the design, maintenance, and reliability of alternative non-distillation approaches for making WFI-quality water, but also to collect viable data from engineering end users so that the discussion could be removed from private unpublished anecdotes and brought to light – for better or worse – for eventual public dialogue among the industry, compendia, and regulatory groups.

Typically, past discussions centered about the topic of "distillation vs Reverse Osmosis (RO) and/or UltraFiltration (UF)" as the final step and arbiter of microbiological and endotoxin control in WFI production. The current survey asked a series of different questions. Instead of focusing on the final purification step, the entire water system design, its operation and control strategies, and testing data was studied.

Of the non-distillation systems that met all of the testing attributes of WFI, though validated as another type of water system, the analysis of the results shows a fascinating variability in the number and types of purification system designs, distribution designs, and sanitization strategies. The analysis also demonstrates that the goals of the survey were met, which were: 1. to expand the discussion to consider the entire water system and 2. achieve a meaningful dialogue based on data of real water systems.

Background

The final purification step in the production of Water for Injection, i.e., WFI, is largely relegated to distillation, and distillation is estimated to be the final step in > 99% of WFI systems for manufacturers for US, EU, and Japan markets. The motivation for the nearly exclusive use of distillation is due to pharmacopoeial standards, regulatory expectations (perceived or real), and the industry's history and inertia. Historically, distillation was the definitive purification process for removing pyrogens from the water.

Standards setting bodies such as the USP, Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and European Directorate for the Quality of Medicines (EDQM) have provided some specificity regarding the production of WFI. Until 2004, USP permitted the use of distillation or Reverse Osmosis (RO) as a final purification step. Since 2004, USP has revised the allowable methods of production to "distillation or a purification technology that is equivalent or superior to distillation in the removal of chemicals and microorganisms." In Japan, the PMDA allows the use of distillation or RO and/or UF; however, recent surveys in Japan have reported that RO/UF is rarely utilized. Ph.Eur. requires the use of distillation exclusively in the

production of WFI although the use of RO is permitted to make Highly Purified Water, a compendial water that meets the same chemical and microbiological requirements of WFI, but has its usage restricted to limited processes and products according to EU law.

Other historical factors are necessary to be included in the discussion:

- Distillation is generally recognized as a gold standard for the removal (separation) of micro-organisms.
- Distillation has been the standard/default final purification step to make WFI. The historical performance of distillation is well known.
- The reduction of micro-organisms and their cellular components (pyrogens) comes from a phase change and subsequent separation, in addition to the heat that is applied to kill organisms.
- Membrane systems are described to retain bacteria upstream by mechanical separation which can be flawed, though modern membrane assembly methods greatly reduced this possibility.
- Some distillation technologies are more tolerant to incoming water variability.
- Maintaining microbial and endotoxin control after the water is produced is as important as the water purification process itself, regardless of the purification process used.

As a result, deviations by the industry from accepted norms are considered risky, and the life sciences industry is well-known to historically be averse to risk.

History

The introduction of water was in the first USP in 1820. Aqua Distillata was described as "Aqua distilleteur vasis permundis, donec ejus duo circiter trientes stillaverint. Aquam distillatum in lagena vitrea servato." Translated – "Let water be distilled in very clean vessels until about two thirds have come over, which is to be kept in a glass bottle." At that time, this was not an official compendium of the US. Nonetheless, it is noted that the water definition describes the method of preparation and storage, yet there are no tests to ascertain the quality of the water. Chemical tests for chloride, sulfate, calcium, and several other common water impurities were eventually included beginning in the 1860s.

The first WFI monograph (Agua pro Injectione) was presented in USP XII in 1942, likely as a result of the effort for World War II. The monograph called for water to be produced by distillation, packaged, sterilized, and tested for pyrogens (USP <151>), in addition to the chemical tests. At that time, distillation was the only known method of removing pyrogens when applied properly.

Today, all pharmacopoeias have specific requirements for the production methods of WFI. This is an unusual phenomenon in the major compendia since the pharmacopoeias typically only specify the identity, purity, and strength of an excipient, drug product, or drug substance. The pharmacopoeias do not – as a rule – describe how to produce an excipient, drug product, or drug substance. This is left to private filing between a producer and regulatory authorities. WFI remains the exception to an otherwise very consistent pharmacopoeial rule.

The net result has been that, especially for global producers, a distillation system was a virtual requirement as the final step in the production of WFI. This would meet all compendial and regulatory standards with the least amount of resistance or controversy.

Today

In recent years, there has been discussion and commentary among various professional organizations, seminar meetings, and standards-setting groups about the potential for other technologies to offer safe and consistent and potentially cost-effective production of WFI. Various motivations for this discussion are included here:

- Green Engineering. The motivation here is to use a smaller carbon footprint by using less heat, electricity, cooling water, etc… As total cost of ownership (capital, cost of operation, cost of maintenance) is prevalent in engineering discussions, additional consideration is given to the drain on natural resources.
- Open technologies. It is reasonable to assume that the desire of the industry is to apply the minimum amount of restrictions while maintaining product and human safety. Any restrictions that can be removed are potentially beneficial to the patient in the form of lower costs, wider distribution, and faster drug discoveries. Limiting the production of WFI is a form of a restriction. This also may serve as a barrier to innovation.
- Advances in materials of construction for membrane systems allow the possibility of hot water sanitization.
- Emerging precedent. Recent papers have gone on the record to demonstrate that the use of non-distillation methods can produce WFI quality water consistently.[1,2]
- Engineering versus academic argument. This is a discussion that is more philosophical than practical, but both positions are based on some fundamental principles. The academic argument is based on the fact that distillation is fundamentally and inherently better than other technologies since 1. distillation involves a phase change and separation, whereas other membrane-based processes are subject to mechanical failures, 2. distillation is always hot, and 3. distillation is more robust and less susceptible to failure than any other technology. All these points are generally accepted and accurate, but with the caveat that distillation can fail if it is not designed, utilized, and maintained properly. The engineering argument is "don't tell me how to make it, just tell me the quality attributes that the product needs to achieve." This is consistent with the discussion point above about not restricting technologies and a potential barrier to innovation.
- Ultimately, total cost (or cost/volume produced) becomes a factor. The costs include those cited above – engineering design, capital, cost of

labor and materials for operation and maintenance, sanitization costs, instrumentation, and testing to meet the peak and average demand to sustain operations. Other costs also will consider expansion possibility, cost of production shutdown, water usage, and risk assessment of impact to final product.

In addition, in past years, the USP Pharmaceutical Water Expert Committee has considered the benefits and concerns regarding the practical aspects of implementing a "no technology limitation" into the WFI monograph. The points above that are related to product safety, quality, and consistency were reviewed. A significant consideration was the fact, even though the USP modified the WFI monograph in 2004 to indicate that WFI "is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms," the overwhelming majority of water producers prescribe distillation either to meet the European market requirements to meet internal corporate standards or to avoid regulatory resistance.

In parallel with these discussions, there have been other discussions at other compendial groups. The most controversial paper, and the genesis of the USP/ISPE survey, was published in 2008 when the European Medicines Agency (EMA) produced a "Reflection Paper on Water for Injection Prepared by Reverse Osmosis."[3] In this paper, the inspection agency presents its views on "why it is currently not considered acceptable to use reverse osmosis for the production of water for injections" and that the paper aims to stimulate further discussion on the topic. The paper is focused on the merits of distillation versus RO insofar as microbial and endotoxin controls are concerned. Little is said (for or against) regarding the chemical controls. The statements in the reflection paper are controversial, as reflected in some of the responses published in PDA Letter.[4] As a result of this type of public feedback, the EMA eventually followed up with an industry survey (not the subject of this paper). This survey requested specific feedback about specific statements made in the reflection paper and to provide references or data to disprove the Reflection Paper's statements.

USP/ISPE Survey Rationale

The position we hold is that the issue of "distillation versus RO" is the wrong question to consider. While distillation has a robust and long history of operation in the production of WFI, it is not perfect or fail-proof, as is sometimes perceived to be the case. The discussion should not be focused on the last step in the water purification process; rather it should be on the "system" as a whole. In this case, "system" is the entire water generation hardware (pre-treatment, purification, distribution, controls, and instrumentation), the sanitization system, and maintenance practices. It is the entire "system" that determines the robustness and consistency of the water production process and the water quality.

To validate this position, we conceived a strategy to prepare a survey whose questions would generate industry feedback on water systems currently in use that make WFI-quality water. The survey includes several questions regarding the normal performance statistics of the water system. Some examples include:

- What is the normal/typical cfu counts per 100 mL?
- What is the normal/typical Endotoxin units per mL?
- How many years has this system been in operation with this level of control?

We also included non-numerical questions such as:

- What is your water source type?
- Indicate all uses of your water.
- If you had to restore micro/endotoxin control to your generation/distribution system, what remedial sanitization methods would be used?
- What are the complete order of unit operations in your entire pre-treatment, purification, and distribution system?

It was questions such as the latter two that would allow us to gain insight about the details of the water "system" and not just the last step in the process.

The second part of the strategy was to find the means to acquire the data from the largest possible pool of potential respondents with such non-distillation WFI-quality water systems. The ISPE Critical Utilities Community of Practice was the ideal source to acquire the data. The CU COP has a strong following of more than 3,300 members. The engineers that use the site have access to the micro/endotoxin data (so does QA), but the water engineering group understands the purification system, the sanitization methods and frequencies, the remedial methods, the hardware changes, and more. The CU COP Steering Committee approved the strategy, and the ISPE administration provided extensive survey tools to assist the authors in developing an online

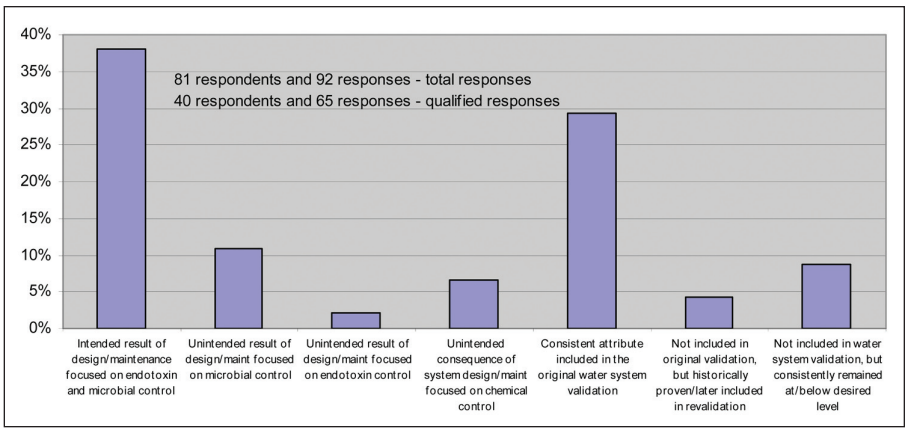

Figure 1. Responses to survey question 1.

survey with a simple user-friendly interface. We beta tested the survey on a few parties, and then the ISPE CU COP Steering Committee released the survey to the entire CU COP.

After a reasonable response period of several weeks, the raw survey response data was compiled by ISPE staff and provided to the authors for in-depth analysis.

Results of Survey

Question 1. For non-distillation based endotoxin controlled system, the level of endotoxin/ microbial control it achieves is (check all that apply).

Of the survey responses to this question (Figure 1), the majority of the systems were designed with the intention to achieve, or originally validated to achieve, endotoxin and microbial control that is consistent with WFI specifications. The minority responses indicate that such WFI specifications were also met, albeit unintentionally, and maintained consistently.

The distinction between total and qualified responses is based on the fact that:

1. Every respondent did not answer every question so there are a variable number of respondents for each question.
2. Some survey responses were too incomplete to be usable with crucial questions aimed at revealing system reliability left unanswered.
3. Some survey responses were completed for distillation systems or did not describe the system unit operations at all; these were omitted since the purpose was to gather data on non-distillation-based systems.

The remaining graphs are for qualified responses only.

Question 2. The endotoxin levels from this water system meet:

These qualified responses (Figure 2) show that these water systems can meet WFI specifications consistently.

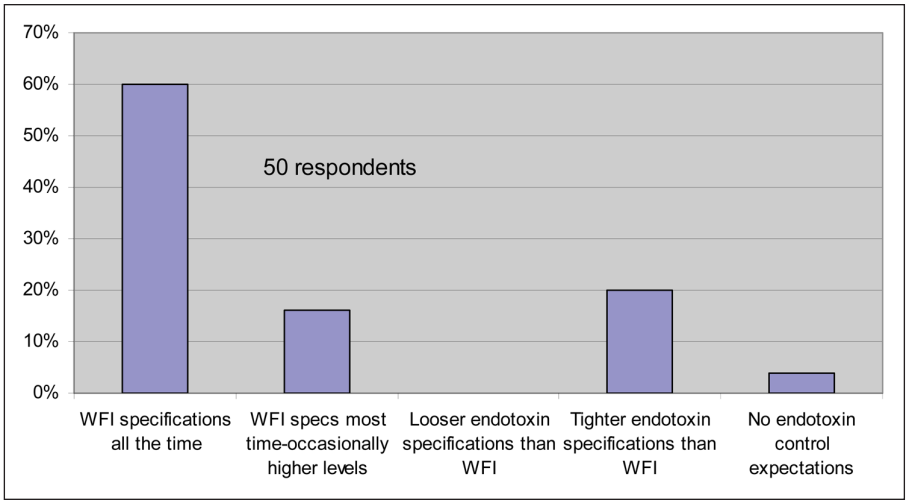

Figure 2. Qualified responses for survey question 2.

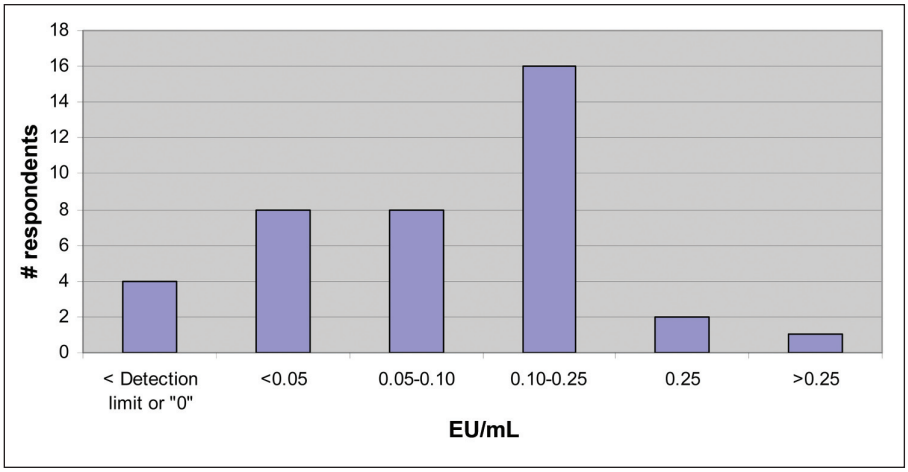

Figure 3. Qualified responses for survey question 3.

Specification	Respondents	Comment
less than "less than 0.25"	4	Responses were 0.03, 0.125, 0.125, and 0.2 EU/mL
less than 0.25	29	Responses were 0.25 EU/mL or < 0.25 EU/mL
more than 0.25	3	Responses were 0.5, 0.5, and < 1 EU/mL

Table A. Qualified responses for survey question 4.

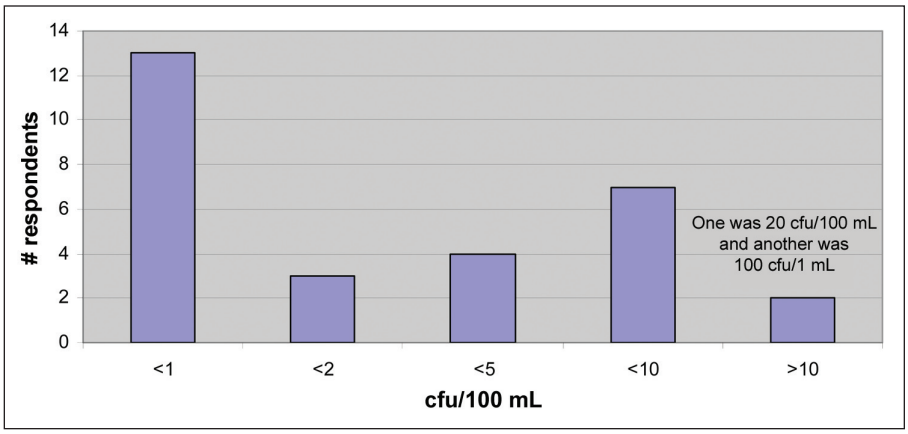

Figure 4. Qualified responses for survey question 5.

Question 3. Indicate your TYPICAL value in EU/mL.

These responses (Figure 3) quantify the results from Question 2 with specific typical Endotoxin results.

Question 4. Indicate your Endotoxin specification.

More than 90% of respondents (33/36) are testing to WFI specifications for endotoxin control, despite not being validated as a WFI system - *Table A*.

Question 5. What is the typical microbial count in cfu/100 mL?

Analogous to the Q4 endotoxin question, > 90% of the respondents (27/29) are achieving microbial test results that meet recommended action levels for WFI - *Figure 4*.

Question 6. While still achieving the level of endotoxin control noted above, indicate how often you have exceeded a bacterial level of 10 cfu/100mL with Gram negative bacteria?

See Table B for responses.

Question 6a. Were these Gram negative bacteria identified?

See Table C for responses.

Question 8. If you had to restore endotoxin or microbial control in the distribution system by remedial sanitization of the distribution system, please indicate which remedial approaches were or would be used (indicate all that apply).

See Figure 5 for responses.

Question 8b. If you had to restore endotoxin/microbial control in the finished water by remedial approaches within the purification part of the system, indicate which remedial approaches were used?

There is no single approach taken to

Response	Respondents	%
Never	18	42.9
Once or Twice	19	45.2
Sporadically (indicate frequency: times per month)	5*	11.9
*1 respondent indicated 4 in 3 years, 2 respondents indicated 1/month, 1 respondent indicated 6/month, another no reply.		

Table B. Qualified responses for survey question 6.

Response	Respondents	%
No	28	75.7
Yes, explain*	9	24.3
*There were 6 responses with details: 1. various Pseudomonadaceae 2. Pseudonoma. Ralstonia insidiosa, Stenotrophomonas maltophilia. Sphingomonas echinoides. Mostly associated with one user point only. 3. > 0.8 CFU/100ml 4. Ralstonia Pickettii 5. Ralstonia Pickettii 6. Acinetobacter baumannii, Sphingomonas paucimobilis, Brevundimonas diminuta, Pseudomonas boreopolis, brevundimonas species		

Table C. Qualified responses for survey question 6a.

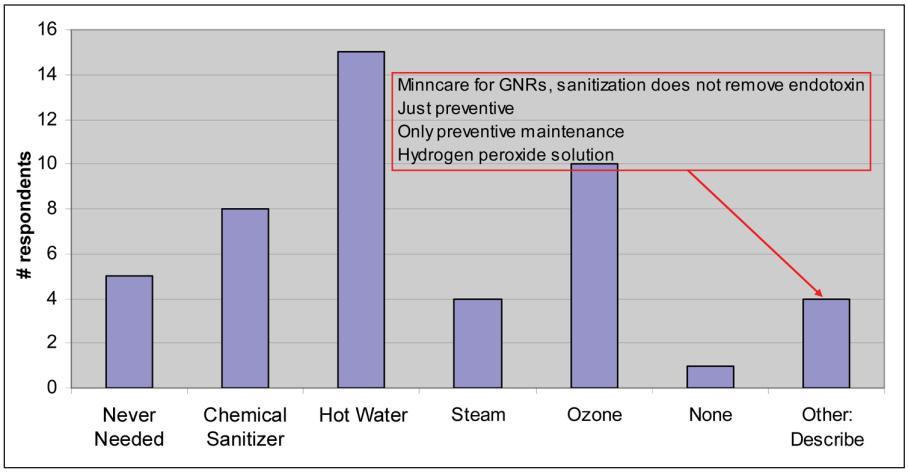

Figure 5. Qualified responses for survey question 8.

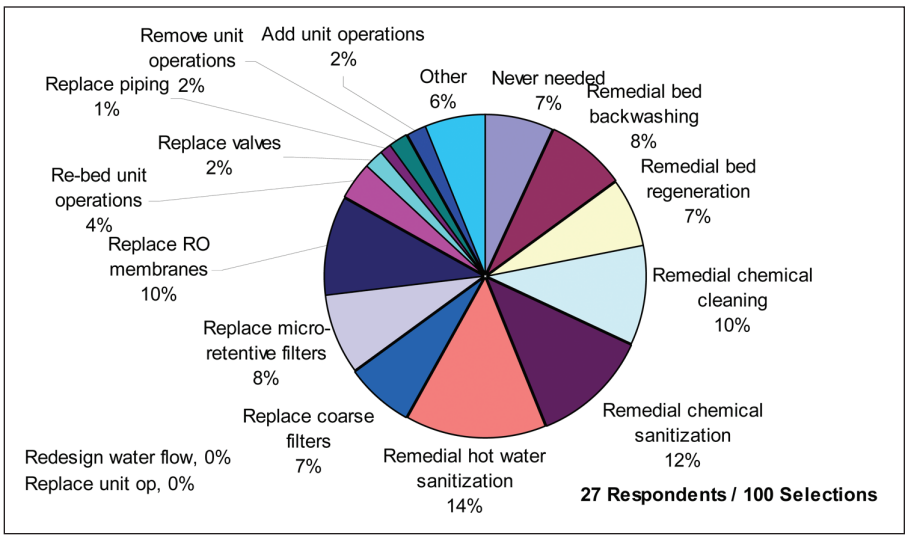

Figure 6. Qualified responses for survey question 8a.

restore microbial control, despite the common notion to apply heat. A variety of methods are used to control the bacteria/endotoxin range from various common sanitization methods to backwashing and regeneration to replacement of filters/membranes - *Figure 6*.

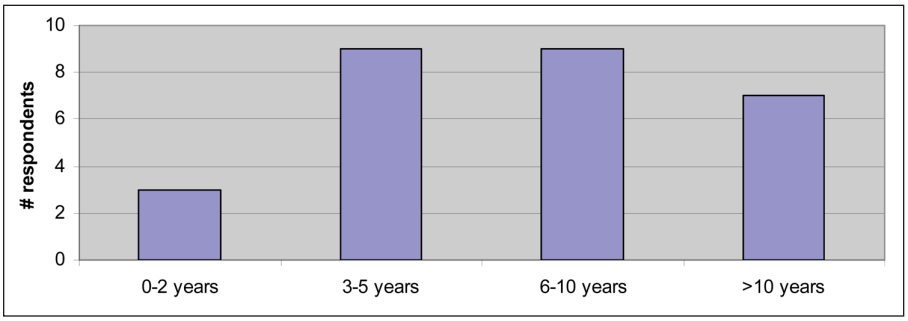

Figure 7. Qualified responses for survey question 9.

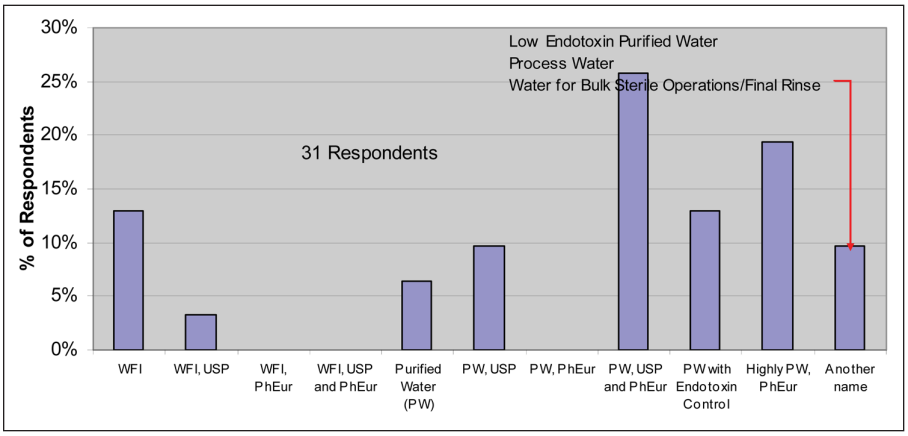

Figure 8. Qualified responses for survey question 10.

Question 9. How many years has this water system been operating with this level of endotoxin control and microbial control?

The survey results shown in Figure 7 indicate that the majority of the responses are from mature systems, albeit far from the intended life (assumed to be 20 years).

Question 10. What is this water grade officially called?

See Figure 8 for responses.

Question 11. Please indicate all uses of your endotoxin/microbially controlled water that apply.

The number of responses (Table D) indicates that water is multi-functional at each site, though cleaning processes and feed water (to other devices) are most prevalent.

Response	#	%	Response	#	%
Human Drugs	19	8.0%	Excipient Manufacturing	2	0.8%
Veterinary Drugs	4	1.7%	Bulk Biological Manufacturing or Purification	7	2.9%
Medical Devices	5	2.1%	Rinsing-Based Depyrogenation Process	4	1.7%
Diagnostics	2	0.8%	CIP Process	15	6.3%
Biologics	6	2.5%	Equipment Washing Machine	16	6.7%
Large Volume Parenterals (LVPs)	1	0.4%	Manual Cleaning Process	13	5.5%
Small Volume Parenterals (SVPs)	4	1.7%	Vial or Stopper Washer	5	2.1%
Ophthalmics	3	1.3%	Medical Device Rinsing Process	3	1.3%
Topicals	5	2.1%	Analytical Reagent Preparation	9	3.8%
Homeopathics or Cosmeceuticals	1	0.4%	Sanitant or Sterilant Preparation	6	2.5%
Prescription Drugs	4	1.7%	Cell/Tissue Culture Media Preparation	6	2.5%
NDA or BLA Drugs	2	0.8%	Laboratory Water	8	3.4%
Generic Drugs	4	1.7%	Feedwater for Autoclave	10	4.2%
OTC Drugs	3	1.3%	Feedwater for Pure Steam Generator	13	5.5%
IND Drug Development	4	1.7%	Feedwater for Still	8	3.4%
R&D or Pre-IND Drug Development	8	3.4%	Water for Humidification	3	1.3%
Drug Product Ingredient	3	1.3%	Applications not Requiring Endotoxin control	13	5.5%
API or Intermediate Manufacturing	9	3.8%	Other Applications (50 words or less)	0	0.0%
Total				238	

Table D. Qualified responses for survey question 11.

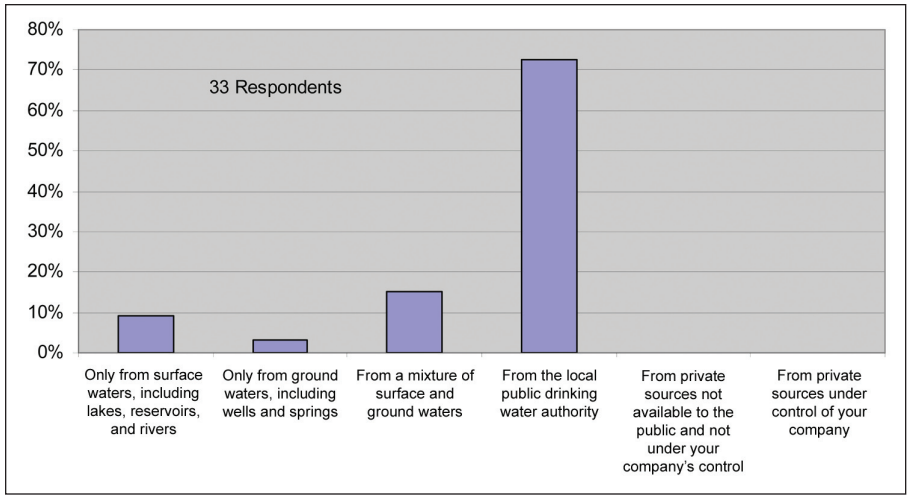

Figure 9. Qualified responses for survey question 12.

Question 12. What is the source of the feedwater for your water system?

See Figure 9 for responses.

Question 15. What is the geographical area where the products made in association with this water are marketed?

See Figure 10 for responses.

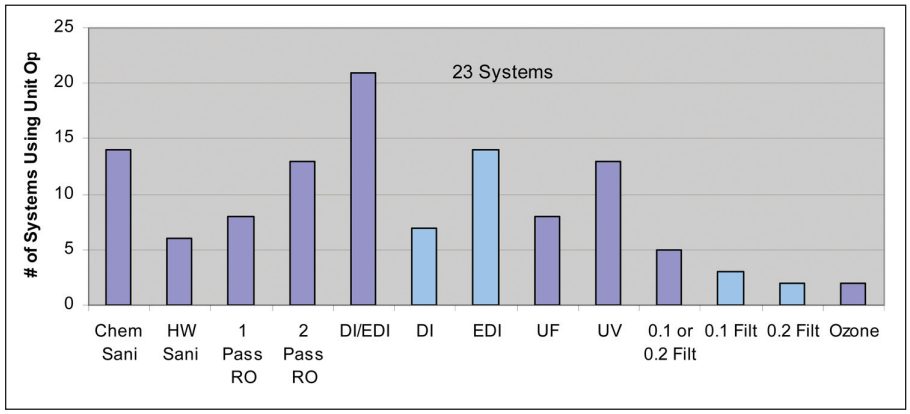

Figure 11. Unit operations used in main purification train.

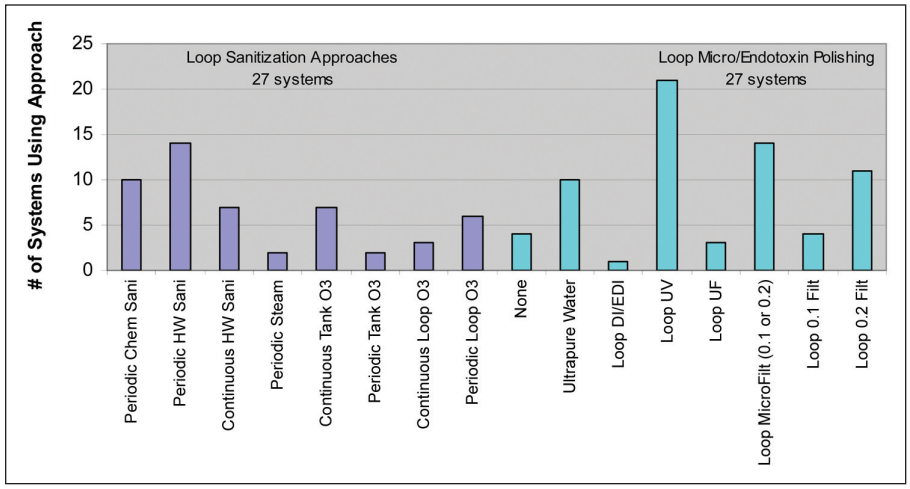

Figure 12. Sanitization/control used in distribution loop.

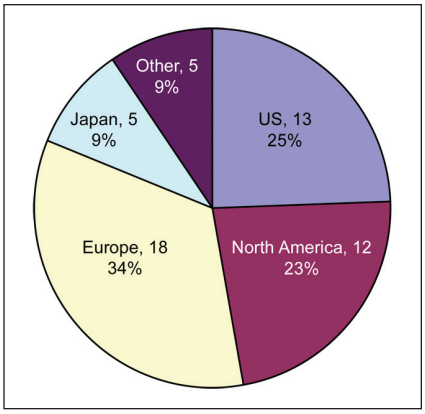

Figure 10. Qualified responses for survey question 15.

Analysis of Results

The following section reviews the survey results and provides a deeper insight into the survey responses by looking for trends, commonality, or consistencies with respect to the design and control of the water system.

Question 13. Describe your purification unit operation sequence here.

This response was submitted in the form of a coded sequence of numbers, where a number was assigned to each possible unit operation, and the sequence of numbers would describe the order of operations of the entire water system, starting from the pretreatment through the primary purification and finally to the distribution system. This data was decoded and then analyzed several ways - *Figure 11*.

In the primary purification loop, as expected, we observed a wide range of unit operations. This includes a large constituency of DI/EDI operations (21 of 23 systems). We also observed a surprisingly high number of chemical sanitization approaches compared to hot water (more on this later).

Question 14. List the sanitization methods used in your water system.

The graph examines the survey for detailed responses to the sanitization control in the distribution loop - *Figure 12*.

In a graph prepared from digging deeper into the survey responses, the combination of primary purification

methods and various sanitization strategies are examined. The message in the following graph is that there are multiple approaches to producing well controlled WFI quality in the purification system. Many combinations using chemical sanitization are shown in Figure 13.

Combining sets of data into broader categories results in the next graph - *Figure 14*. While there was a high degree of use of individual methodologies (heat or chemical or ozone), there was an ample set of users who applied multiple techniques.

A different analysis of the same data focused on the purification control methods of UPW (it is considered control by starving or greatly slowing microbial growth), ultrafiltration, UV, and microfiltration. These four control methods, and combinations thereof, demonstrate a wide diversity of endotoxin and microbial control methods - *Figure 15*.

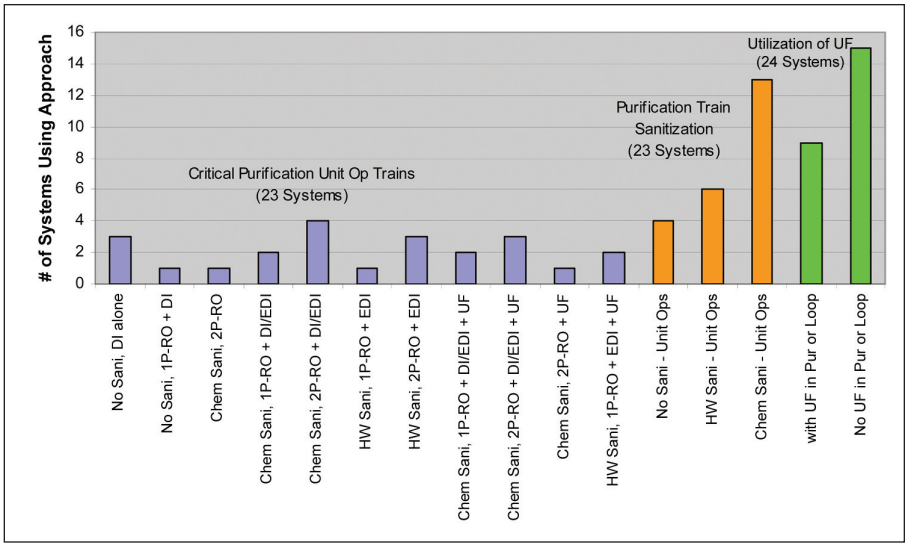

Figure 13. Critical purification train combinations and properties.

Note: Due to the categorization, a single water system could fit into multiple categories. For example, a system with UV, UF, and microfiltration could be assigned to three categories: UF+2 others, UV+2 other, microfiltration+2 others.

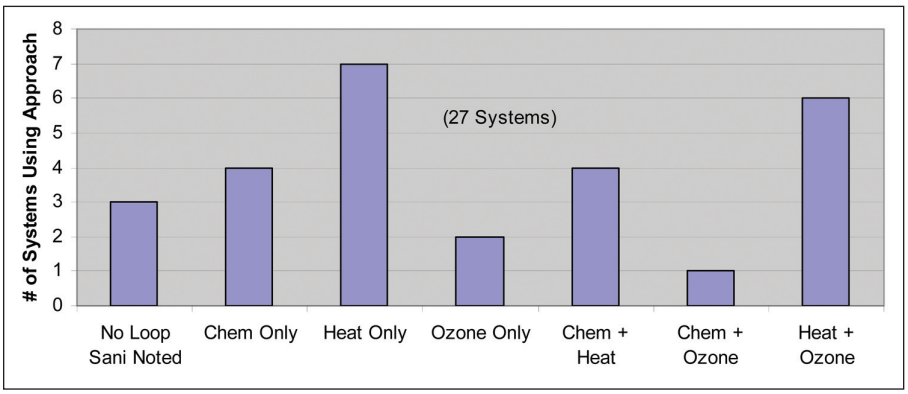

Figure 14. Loop sanitization combinations.

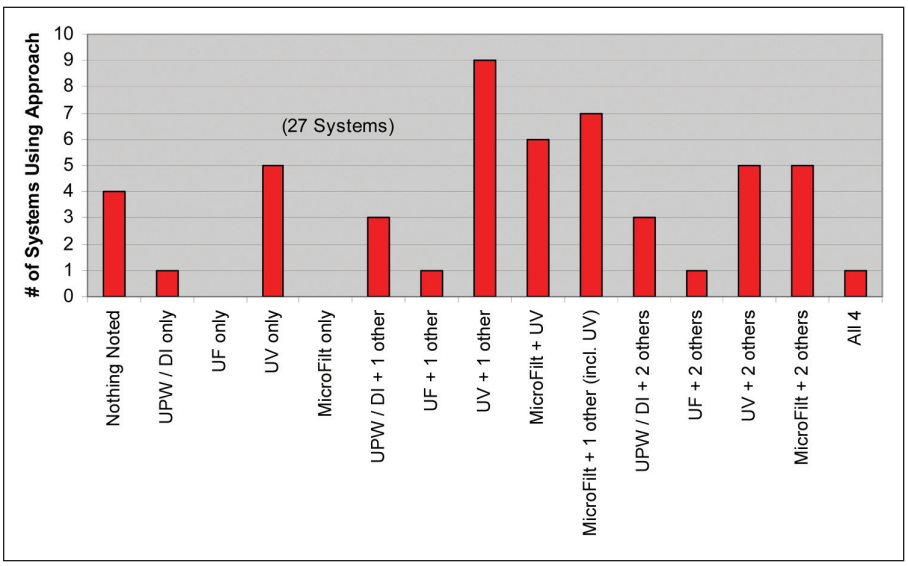

Figure 15. Loop micro/endo control/polishing combinations..

Conclusions of Survey and Analysis

In recent years, a common discussion in pharmaceutical water circles has been "can you make WFI quality water using methods other than distillation?" A typical answer to this question may have been "standard pre-treatment with continuous hot water utilizing 2-pass RO, electro-deionization, UV, and ultra-filtration." This basic design concept – with many details not listed here – could provide the necessary purification steps to reduce the ionic and organic chemical impurities, microbes, and endotoxins to meet compendial expectations. However, in the survey results and analysis, we reached a set of conclusions that did not meet some of the previously held expectations.

The primary conclusion that we make is that there is not one single approach to achieve the target of reliably producing WFI by alternative methods. Rather, it is evident that there are multiple purification sequences, multiple sanitization methods, and multiple microbial/endotoxin control strategies, and there is no overriding commonality in the design or microbial/endotoxin mitigation strategy. To substantiate this point, we review the following results

of the survey.

First, there was little commonality in the system design. We would find that 1-pass or 2-pass RO with DI (or EDI) was common, but this was not exclusive. There were multiple exceptions to this design, including the use of DI without sanitization in the generation system or the use of DI without the use of RO. The latter were in the minority, but the fact is that there are multiple design approaches to make WFI quality water.

Second, in this survey, the number of chemically sanitized systems exceeded the number of hot water sanitizable systems. Though the number of surveys is not statistically significant to interpret this point quantitatively, the fact that hot water sanitization was not the dominant method further emphasized the lack of commonality in successful water systems.

Third, the number of systems utilizing UF was roughly equivalent to the number of systems that did not. It was clear that RO and perhaps EDI/DI were effective at maintaining endotoxin control, in combination with effective biofilm reduction strategies.

Next, in the distribution loop, the use of hot water was greater than the use of chemical and ozone sanitization. But again, this reinforces the argument that there are a multitude of approaches to produce these waters with sufficient microbial and endotoxin and chemical control.

We do see that in the generation and distribution loops, there are multiple purification steps used for microbial and endotoxin control. Combinations of UPW/DI, UF, UV, and microfiltration were used in the polishing loop. Multiple sanitization methods including combinations of heat, chemicals, and ozone were used.

As a result of these analyses, the conclusion we continue to reach is that there are multiple approaches to achieve WFI quality. There is not one type of unit operation sequence or loop polishing design or sanitization strategy that would necessarily work. Instead, we found a distinct lack of consistency in these surveyed systems, or in other words, no silver bullet or predefined recipe to achieve the necessary microbial and endotoxin control. Rather, it is a holistic and systemic view by the water system designers and owners that the entire water system design, purification strategy, sanitization strategy, remedial sanitization programs, and backup plans are necessarily integrated to achieve the desired result, but not isolated to a single approach. No doubt, some of these approaches required more diligence than others in maintaining WFI-quality water, but they nevertheless have demonstrated that they achieved that goal.

At a recent EDQM Workshop, a controversial concern was voiced regarding the possibility that membrane-based purification approaches could generate biofilms with unknown biological toxins, other than endotoxins, and thus adversely affect the water. The concern was amplified when it was suggested that these types of unknown toxins would have been eliminated by distillation-based purification. This potential phenomenon calls into question the adequacy of the long-standing and proven WFI specifications that focus on control of chemical and endotoxin contaminants. Though the production of other toxins by mature, uncontrolled biofilms in aquatic environments is theoretically possible, their presence in water systems (whether using distillation or not) is unsupported. Therefore, it is speculative to be concerned about a hypothetical contaminant, especially where its potential source, biofilm, is being actively controlled. The current WFI specifications that focus on chemical and endotoxin control (which relate closely to microbial control) have proven to be adequate specifications for this water, regardless of how it is produced. Therefore, these USP/ISPE survey results have relevance to the stated goal of an open public dialogue of suitable alternative, non-distillation methods of making WFI.

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4. *PDA Letter*, Vol XLIV (7), pp 15-16.

Acknowledgements

It has been our quest to have an open discourse on the subject of alternative (to distillation) methods to produce WFI, without advocating for any technology. We took the approach that we needed to acquire highly detailed engineering data about the water system from knowledgeable parties. We needed input about the engineering of the water system, the quality data, and sanitization and remediation methods. To do this, we knew the ISPE Critical Utilities Community of Practice (CU COP) would be the ideal forum to seek the data, and we validated that idea with the Steering Committee of the ISPE CU COP. Additionally, ISPE Staff and the ISPE COP leadership supported the initiative and provided extensive resources and hours of support to help us create the online survey in a way to make the data analysis possible. Finally, we thank the USP staff and management (too many to name) who encouraged our initiative, supported our costs, and permitted us the freedom to design the survey and present the results in various forums.

About the Authors

Dr. Anthony Bevilacqua is the Head of R&D at Mettler-Toledo Thornton. Dr. Bevilacqua earned a PhD in physical and analytical chemistry at Tufts University. For more than 25 years, Dr. Bevilacqua has been active in the development of analytical techniques, specializing in ultra-low-level detection systems and high purity water impurity analysis. He is also active with the ISPE as a Steering Committee member of the CU COP, and he is also active as a participant and organizer of seminars with ISPE, PDA, and other organizations

internationally. Dr. Bevilacqua was a technical contributor to development of methods and limits for the USP <645> Water Conductivity, he was elected as the Chair of the first USP Pharmaceutical Water Expert Committee from 2000 to 2005 and 2005 to 2010, and he is currently elected to the USP Chemical Analysis Expert Committee for the 2010 to 2015 cycle. Dr. Bevilacqua has been a regular contributor to multiple ISPE Baseline and Good Practice Guides. He may be contacted by email: anthony.bevilacqua@mt.com.

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Efraim Cohen-Arazi discusses the business side of the life sciences industry. He offers a look into the R&D and investment strategy of his own venture investment firm, Rainbow Medical.

PHARMACEUTICAL ENGINEERING Interviews

Efraim Cohen-Arazi, CEO and Co-Founder, Rainbow Medical

by Nissan Cohen, ISPE *Pharmaceutical Engineering* Committee (PEC) Member

Efraim (Efi) Cohen-Arazi is CEO and Co-Founder of Rainbow Medical, a venture investment firm that seeds and grows companies that develop breakthrough medical devices. Cohen-Arazi has more than 20 years of experience in the medical and biotech industries involving executive management responsibility for both development and business. Prior to establishing Rainbow Medical, Cohen-Arazi served as CEO of InterPharm, Israel, a company specializing in drug development and delivery. Previously, Cohen-Arazi was VP Corporate Manufacturing, Head of Contract Manufacturing and Site Head at US-based Amgen Corporation, where he established and led several global strategic partnerships to develop and manufacture small molecules and biopharmaceuticals. Cohen-Arazi held senior positions at Immunex in the US and at the Merck-Serono Group in Switzerland. Cohen-Arazi holds advanced degrees in agriculture and microbiology from the Hebrew University of Jerusalem.

Q Efi, tell me a little about your background in Israel before you came to the United States.

A I studied at Hebrew University in Israel and received both my BS and MS in agriculture and microbiology. After graduation, I started to work in vaccine production and development.

Q How did you get involved with the pharmaceutical and biotechnology industry?

A Initially, I started work in vaccine production with an Israeli firm known as ABIC. I left ABIC to work for InterPharm, the Israeli subsidiary of the Ares Serono, the Swiss biotech company. After seven years with InterPharm, I was hired by Serono to build a new biotech center in Switzerland in 1994. The Ares Serono facility in Switzerland was a fabulous, but unusual project at the time because the schedule allowed 34 months from groundbreaking to initial production. This was an extremely fast tracked project which incorporated for the first time in our experience total planning and integration of design, planning, construction, commissioning, and validation.

Q How was this accomplished?

A From the beginning, we (Serono) decided to work very closely with our design firms and suppliers. We actually implemented the concepts of QbD before the terminology was defined in the pharmaceutical industry. Working with well-known A&E, construction, and sub-contractor firms we were able to align our various departments to have seamless documentation and goals. The coordination included our engineering, validation, operations, production, QC/QA, and project management departments working very closely with the design and construction firms. Understanding the needs of the biotech production facility coupled with an excellent game plan of how to coordinate and work with A&E, construction, and suppliers helped define our course. Additionally, complete, useful, and mandated

documentation helped bring the Ares Serono facility to operational status in the very short time of 14 months. But most importantly was the team that we put together to lead this project – a wonderful, professional, and dedicated team that worked hard and continuously innovated to make this accomplishment happen.

Q How have the transitions in biotechnology applications affected the pharmaceutical industry as a whole and specifically your career?

A After working at Serono in Switzerland, I moved to Seattle and became the Senior Vice President of Operations at Immunex. Immunex, at that time, faced a serious production capacity constraint and was in need of radical thinking to develop the proper process modules for biotechnology production in house, while expanding contract manufacturing capacity. Using knowledge gained at Serono, Immunex Operations was revamped in a very short time period with a clear roadmap to eliminate the production capacity constraints. While at Immunex, I was also responsible for the refurbishment and construction of the biotech site in East Greenwich, Rhode Island. This mega-facility was an investment of more than $1 billion and was designed, built, and operational on an accelerated schedule. In our experience, this was the largest single biotechnology production site ever commissioned. Immunex was subsequently purchased by Amgen and I became the Vice-President of Amgen.

Q Having lived in both Israel and United States, I understand some of the emotional issues of being away from Israel. Could you comment?

A While at Amgen in the mid-2000s, my immediate family was in Israel while I was working at Amgen in the United States. Traveling back and forth between the United States and Israel is not only tiring, but emotionally draining. Amgen knew I needed to extricate myself from the situation. I became an Amgen consultant and continued my relationship with the organization.

Q Your current company in Israel is Rainbow Medical, a venture investment firm. How do you evaluate prospective companies seeking investment?

A Our firm is funded by and is an active participant in the medical device and medical technology markets. We have investments from many "big pharma" companies and keep a "pulse" on the industry's needs. Our strategy is a "search and find" investigation. We listen to our investors about the therapies, product development, and developments needed in the industry. Many large corporations do not have the innovation and core competency, internally, to develop new and cutting edge technologies. Rainbow Medical "finds" and invests in cutting edge therapies, technologies, and innovations that may be integrated into a "big pharma" operation at a later date. We have invested in more than 10 firms in Israel which have tremendous potential.

Q How has the consolidation of the industry affected product development, clinical trials, and introduction of pharmaceuticals or therapies?

A The industry as a whole has been constrained by the FDA. The product development and approval process in the United States is long and tedious. Many companies are concentrating on Europe for product development and clinical trials. Companies are going to Spain, Ireland, and areas of Eastern Europe specifically to conduct clinical trials. This usage of European clinical trials has reduced many of the development-to-clinical cycle times, in some cases, to less than five years. This is a vast improvement over the development-to-clinical cycle in the United States.

Q Many medical devices have been developed in Israel, including artificial skin, surgical lasers, and artificial limbs. Do you concentrate on a particular sector of the medical device industry either locally or globally?

A Our emphasis is primarily on developing therapeutic medical devices in Israel. Israel has a long history of medical device development, some of it due to the advances in the defense industry and infrastructure and some due to war injuries and needed therapies for rehabilitation. Many devices are developed due to the intertwined nature of medicine and science which is prevalent in Israel.

Q When assessing a company seeking financing, how are the real and potential products strategically evaluated? Do you assess the manufacturability of the proposed product or technical hurdles to production?

A Using our background at Rainbow Medical, we work closely with these companies to assess all aspects of the potential product, not just its development. Manufacturability, technology transfer, clinical production, production process modules, and critical technology parameters, etc., are all assessed using the expertise of Rainbow Medical.

Q Does Rainbow Medical help the developing company with expertise or suggestions in manufacturing or technology transfer for clinical testing?

A Yes, especially for startups. Founders are often saddled with fundraising to keep their operations solvent. This diminishes the research at the start-up company as many founders of start-ups are the technical expertise of the company. Concentration on the founder's core competencies of research rather than fundraising and private placements will help the start-up thrive.

Q What is the typical time duration in years, from a company seeking stage one funding until clinical trials? Is it five years, 10 years, or longer?

A It really depends on the sector within the life science industry.

In medical devices, it sometimes can take two to three years while in the pharma/biotech it sometimes can take five to seven years to get to clinical trials. But as noted above, the regulatory environment can stifle cycle time for development-to-clinical trials. Europe is a better regulatory environment.

Q Do you foresee the development of small innovative entities that only work on an R&D basis, eliminating many large budgets of pharma/biotech companies, with either exclusivity or non-exclusivity to large multinational pharmaceutical companies?

A Yes, especially in Israel, as research and development are high priorities and innovation is one of the strengths. Other industries have invested in Israeli hi-tech R&D. Significantly, the American semiconductor industry has many R&D facilities in Israel. The quality of R&D firms in Israel is very strong, but commercialization has not been a great forte. The interleaving of Israeli R&D with European and American "big pharma" can be a significant business model and venture.

Q What are the frontiers of the life sciences industry over the next 10, 20, and 30 years?

A In the longer term, I foresee a few trends:

a. big pharma companies entering deeper into the medical devices area

b. big medical devices concerns entering into software and telecommunications

c. the creation of a world wide web based healthcare system

d. biotech and medical devices companies' collaboration to target drug delivery

e. increased use of MicroElectroMechanical Systems (MEMS) and nanotechnology in the medical devices

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Alternative Test Methodology for In-Situ Testing of ePTFE HEPA Filters for Pharmaceutical Applications

by Eugene Bryan, Bill Kitch, Jim Meek, Dan Milholland, and Nathaniel Nance

This article presents the study results of using an ultra low poly-alpha-olefin (PAO) challenge and a particle counter to preform leak sizing on an expanded polytetra-fluoroethylene (ePTFE) filter.

Introduction

The benefits of expanded polytetrafluoroethylene (ePTFE) filters, including the significant reduction in energy cost, chemically inert, and increased durability, have long been known in critical semiconductor applications.[1] The use of ePTFE filters in pharmaceutical applications is not widely used due to poly-alpha-olefin (PAO) loading of the filters when using the traditional aerosol photometer method for filter integrity testing.[2] Filter failures pose a significant cost to pharmaceutical manufacturers that produce product in a GxP critical environment. The ability to widely use ePTFE filters in pharmaceutical applications would provide valuable financial benefits in regard to lowering energy consumption, reducing production downtime, and reducing repair time, all leading to an increase in operational efficiency and risk mitigation.

In an attempt to solve silicone gel seal degradation by PAO, a test method, long used by the electronics and aerospace industry in Europe and Asia, was evaluated as an alternative approach to conduct filter leak detection in pharmaceutical applications.[3,4] This alternative test methodology was employed as a means to test ePTFE filters under conditions that would not significantly affect filter loading.[2] An ePTFE High Efficiency Particulate Air (HEPA) filter was subjected to the ultra low PAO test method in an attempt to mitigate the effects of PAO loading and establish a basis for the use of ePTFE HEPA filters in pharmaceutical applications with the same methodology of the microelectronics industry. The test method proved successful in determining leak sizes in the ePTFE filter without any of the negative effects of PAO loading. Under this test method, the use of ePTFE could be validated in critical ISO Class 7 and cleaner manufacturing areas where structural integrity and energy savings are valuable. This article gives a summary of the test methods and shares the results.

Background

From the 1960s to mid 1980s, dioctyl phthalate (DOP) was used in concentrations of 80 mg/m^3 (µg/L) to 100 mg/m^3 (µg/L) as an aerosol challenge for leak testing HEPA filters.[5] In the 1980s, aerosol photometers progressed to using solid state electronics and were utilized as a more sensitive instrument to identify filter leaks. With the implementation of these more sensitive and stable units, the recommendation for DOP aerosol challenge concentrations was reduced to 10 mg DOP/m^3 (10 µg of DOP/L) of air.[6] The early 1990s brought a change to the challenge material, due to DOP being labeled as a potential carcinogen. Emery 3004 polyalphaolefin (PAO) was recognized as a non-hazardous replacement and has now become the industry standard.[7]

An investigative study of current filter test methods was conducted to see if the benefits of ePTFE could be realized in aseptic manufacturing environments. When testing an ePTFE ULPA filter with 15 mg/m^3 (µg/L) of PAO, a pressure drop increase of 96% occurred in approximately 5.25 hours at 650 cfm.[2] The study clearly showed PAO exposure on the order of 15 mg/m^3 (µg/L) was detrimental to ULPA ePTFE filters, due to the drastic increase in the filter resistance (pressure drop) with time. This is due to the loading and occlusion of the pores in the ePTFE.

In addition to filter loading, when considering testing of ePTFE filters with the conventional use of PAO as a challenge aerosol, bleed through also was identified as a potential issue. The is-

sue of bleed through may occur when using thermally generated PAO to test ePTFE filters. This is due to the thermally generated aerosol having a 0.10 to 0.45 mass mean diameter, which is closer to the MPPS of the filter. This creates an issue with a photometer measuring a concentration and looking for leaks at or above 0.01%. The bleed through could erroneously manifest itself as an artificially large leak or in some cases, a continuous leak across the filter measuring a 0.025% or less leak rate. The PAO concentration levels discussed in this article are much lower than the standard levels and require generation by cold PAO generation methods.[8]

Cost Savings

The key with utilizing ePTFE is the overall cost savings to the end consumer. The use of ePTFE has several advantages over standard microglass. The best asset in the pharmaceutical environment is the strength of the material. The strength ranges from 10 to 100 times as strong as microglass depending on the carrier substrate that can be modified to an individual application. This creates a filtration media that does not fail under standard operating procedures, cleaning, installing, testing, and provides a durability to mitigate almost all risks of contamination from airflow. The filter will not shed, tear, puncture, or sustain pleat tip separation. Some standard costs associated with this is a replacement filter, labor for installation, letters to the FDA, follow up qualifications/validations, and worst case a recall. The individual pharmaceutical costs vary, but could easily get into the several thousand dollar range depending on the severity of the failure. The amount would be a multiple of the filter cost.

The energy costs also vary depending on electricity cost. An example would be that comparable filters at 2000 cfm would have a $250/year energy savings at $.10/kwh using ePTFE versus microglass. In a terminal filter application that testing was performed on in this article, the filter would save $32/year energy savings. This is not as significant as the risk mitigation savings, but also offers a payback on the additional filter cost during the life of the filter.

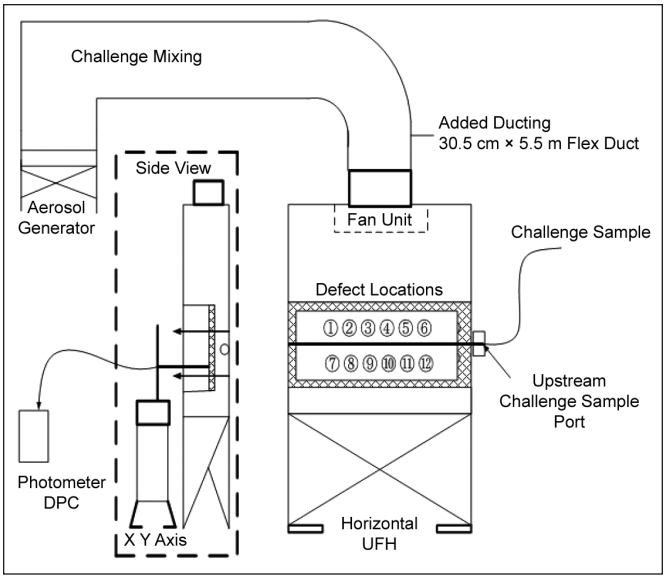

Figure 1. Test setup.

Executive Summary

This engineering study conclusively confirmed utilizing an ultra low concentration PAO challenge as an acceptable form of leak detection on ePTFE filters. This method dramatically reduces the potential of the filter loading issues identified in the prior ePTFE exposure studies.[2] The test method provided a 97+% reduction in PAO exposure to the filter when compared to the currently accepted test methodology outlined.[2] The acceptance and use of ePTFE filters and the ultra low concentration PAO test methods outlined here will greatly enhance the options of utilizing improved technology in pharmaceutical applications. The benefits gained from this will include reduced energy costs and increased operational uptime along with risk mitigation.

Test Overview

The engineering study on the effects of ultra low (< 0.3 mg/m^3 (µg/L)) PAO concentration testing of ePTFE filters was performed at the Baxter BioScience Thousand Oaks location in September 2010 by the authors of this article. The study showed the equivalence and effectiveness of testing ePTFE filters with industry typical concentrations (10 mg/m^3 (µg/L) or greater) and ultra low concentrations of PAO to detect leaks and determine their sizes.

The conventional test method of using a photometer and a ≥ 10 mg/m^3 (µg/L) PAO challenge was employed as a means to size defects created in an ePTFE filter. The results were directly compared to an alternative test method that was composed of using a Discrete Particle Counter (DPC) with a significantly reduced (< 0.3 mg/m^3 (µg/L)) PAO challenge.

Testing was performed by creating 12[1] defects in the HEPA filter of a Laminar Flow Hood (LFH). Comparative test data was then taken using the two methods.

An X-Y axis linear bearing sample probe positioning device was placed in front of the LFH as a means to remove sampling variation due to probe positioning. This unit consisted of a base secured on the floor with movable horizontal and vertical axes for exact probe positioning (±1 mm).

The study was performed using a 610 mm × 1220 mm (2 ft × 4 ft) horizontal LFH as seen in Figure 1. The HEPA filter used for the study was a Type C ePTFE filter, in accordance with IEST-RP-CC001.5, rated for a nominal flow of 630 cfm with an efficiency rating of 99.95% at the Most Penetrating Particle Size (MPPS). The IEST is a recommended practice for all HEPA and ULPA filters between customers and suppliers. The LFH was tested for airflow velocity, leaks, and unidirectional flow prior to beginning the study. Determination of the uniformity of the aerosol challenge was accomplished by fabricating and installing a stainless steel guide upstream of the filter. A sampling tube was then inserted into the guide and positioned so the sample tube opening was located at the end of the guide. A flex duct was attached (30.5 cm (12 in) diameter × 5.5 m (18 ft)) to the inlet of the hood to achieve adequate upstream mixing.

Measurement and test equipment utilized to determine aerosol challenge concentrations upstream of the HEPA filter was a photometer and a laser particle counter in combination

Method	Condition	Instrument	Reported Challenge Measurements
Ultra Low PAO	1	Discrete Particle Counter	~20 × 10^6 ≥ 0.3 μm particles per ft^3 PAO
	2	Discrete Particle Counter	~7 × 10^6 ≥ 0.5 μm particles per ft^3 PAO
Standard PAO Method	3	Aerosol Photometer	~11 mg/m3 (μg/L)
Note: A PAO aerosol produced by a Laskin nozzle of 38 million particles > .3 um is equivalent to approximately .1 mg/m^3 (μg/L)			

Table A. Conditions of test.

with an aerosol diluter. The particle counter and diluter instrument combination was used to determine the actual number of challenge particles for the ultra low level PAO testing (< 0.3 mg/m^3 (µg/L) (conditions 1 and 2)).

Study Conditions

Three evaluated conditions were derived from a combination of the particle sizes (0.3 and 0.5 µm), photometer, and DPC test equipment, and the selected aerosol challenge concentrations (PAO). Table A defines the test instruments, concentrations, and particle sizes tested.

Note: A PAO aerosol produced by a nozzle of 38 million particles > .3 µm is equivalent to approximately .1 mg/m^3 (µg/L).

Test Details

Equipment and Materials

- Discrete Particle Counter
- Portable Self Contained Aerosol Generator
- Poly-alpha-olefin (PAO)
- Photometer
- 2' × 4' Horizontal Laminar Flow Hood
- Aerosol Dilutor
- X – Y Axis Positioning Device
- 12" × 18" Flexible Ducting
- Air Data Multimeter
- Handheld Ultrasonic Aneometer

ePTFE Filter

Defects (12 holes) were made in the ePTFE media by inserting a 30 gauge hypodermic needle into the media twice at each defect site. The average face velocity of 104 fpm (192 m/sec) was determined using the ultrasonic anemometer. The face area of the filter was 6.52 ft^2. The volumetric flow through the filter was calculated to be 675 cfm. Pressure drop across the filter was measured to be 0.16" wc. It was noted this was approximately 25% of the pressure drop of a comparable wet-laid microglass filter (0.58" wc @ 650 cfm) operating at 90% of the airflow volume of ePTFE.

Upstream mixing was verified using a particle counter with ultra low concentrations of PAO as the challenge. Measurements were taken at six locations upstream of the ePTFE filter. The sample locations fell in between the two rows where the defects were created (~4" below and above the first and second rows respectively). The PAO sample reading variance for the six locations was < 1% which is well below the variance limit of ±15% across the challenge area as stated in ISO 14644-3 Section B.6.2.3. as seen in Table B.

The quarter Laskin nozzle generator was used in combination with an aerosol reducer (oil mist eliminator with an 18 gauge capillary bypass) to provide the upstream challenge. Thirty second samples (0.5 ft^3) were taken at each of the six locations and the counts per cubic foot are shown below. The differential pressure of the dilutor was measured at 4.89" wc which corresponded to a dilution factor of 966. The nozzle generator with the aerosol reducer created a filter challenge of approximately 20 million particles at ≥ .3 µm and approximately 7 million particles at ≥ .5 micron per cubic foot of air. The sizing was repeated 10 times to gain statistical significance.

Ultra Low PAO < 0.3 mg/m^3 (µg /L) Challenge using a DPC (Conditions 1 and 2)

The ePTFE Filter was challenged with an ultra low level of PAO in the range of 0.3 mg/m^3 (µg/L), as determined by the photometer. The defect sizes were measured in order starting with defect 1 and continuing sequentially to defect 12. After completing the defect sizing, a new upstream challenge was measured and defect sizing was repeated for a total of 10 runs to give statistically valid numbers.

At the beginning and end of each run, the upstream challenge was recorded. At the end of run 8, it was noted that the upstream challenge was increasing at a significant rate. It was theorized that the increase was related to loading of the oil mist eliminator used to reduce the output of the aerosol generator. Runs 9 and 10 were excluded in the analysis, due to the abruptly rising challenge concentrations.

Standard PAO 10.0 mg/m^3 (µg/L) Challenge using an Aerosol Photometer (Condition 3)

The third condition consisted of utilizing the traditional PAO aerosol/photometer method to size the defects created in the ePTFE filter. The ePTFE filter was challenged with ~10.7 mg/m^3 (µg/L) (average upstream of 10 runs) of PAO using the TEC 1.5 nozzle generator operating at 20 psi. The defect

Sample Location	Counts/ft^3 ≥ 0.3 micron particles	Counts/ft^3 ≥ 0.5 micron particles
1	37890	11224
2	39732	12038
3	39726	12018
4	39484	11868
5	39624	12114
6	38626	11810

Table B. Diluted upstream particle counts at leak detection points.

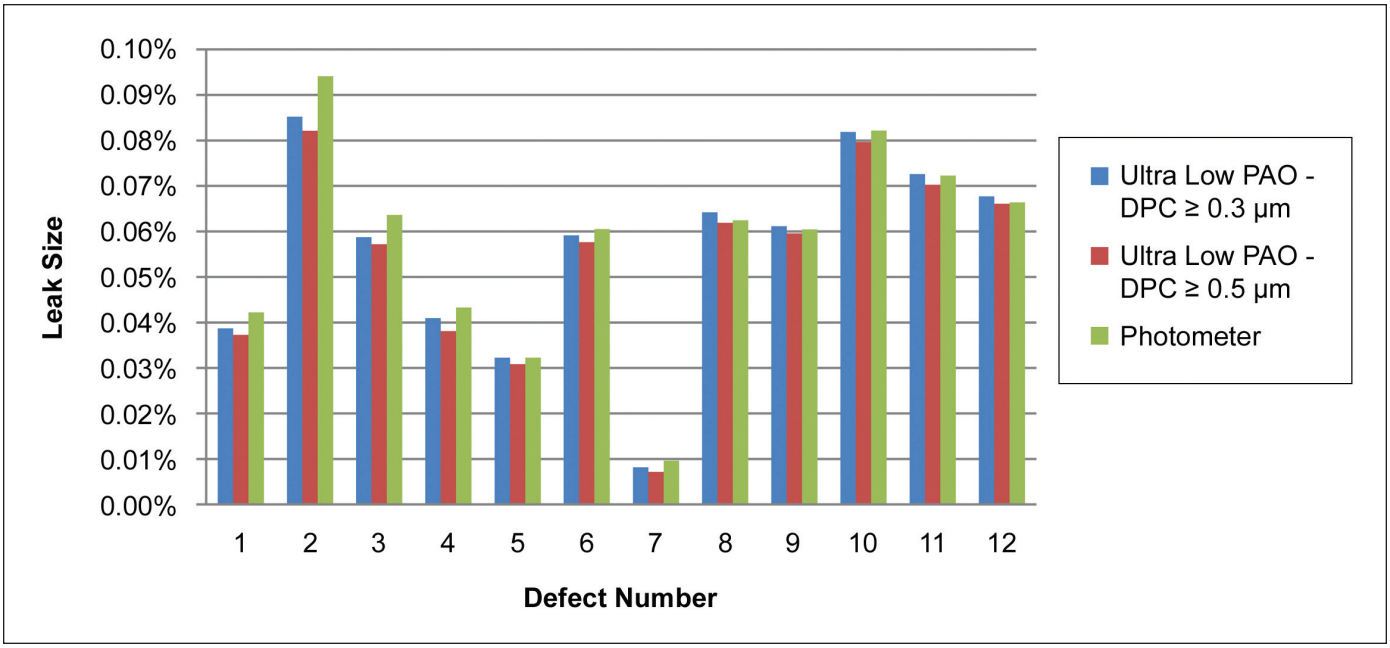

Figure 2. Leak size variation by instrument.

sizes were measured with a photometer in order starting with defect 1 and continuing sequentially to defect 12. After completing sizing for all 12 defects, a new upstream challenge was measured and defect sizing was repeated for a total of 10 runs. The average (over 10 runs) defect size is shown below for each defect 1 to 12.

Summary

The performance of the ePTFE was unaffected during testing. One concern was that the high doses of PAO would affect the outcome of the testing results for which data was gathered over a course of 2 to 3 hrs. The data showed that the ePTFE filter was unaffected by the testing as it maintained efficiency of at least 99.99% and a pressure drop of 0.16" H_2O. This is compared to a capture efficiency of 99.99% and a 0.58" H_2O pressure drop across the glass filter at 90% of the airflow.

The average leak sizes for the three test conditions are shown in Figure 2. A direct comparison of the test method reveals that the particle counter on average sized the leaks slightly smaller than the photometer for both the ≥ 0.3µm and ≥ 0.5 µm particle size distribution conditions.

After reviewing the data presented in Meek's study,[3] it was noted that the particle counter on average sized leaks slightly larger than the photometer. To better understand the repeatability and reproducibility of the measurement and test equipment used in the study, a head to head leak size comparison using 10 photometers was carried out.[9] The same comparison was later carried out using 7 particle counters. The results of the study showed that there was no statistical difference between the leak sizes obtained for the traditional and alternative test methods presented here.

Conclusion

Two test methods were employed to size defects in an ePTFE filter:

- ultra low level (~0.3 µg/l) PAO challenge with a discrete particle counter
- standard level (~10 µg/l) PAO challenge with a photometer

The results indicate that defects in the ePTFE filter can accurately be sized using ultra low level PAO challenges and a particle counter. Under the aforementioned test methods, both DPC test options (≥ 0.3 µm and ≥ 0.5 µm particle count defect sizing) performed adequate in comparison to the photometer.

When comparing both the initial study[3] and this article, the variation of sizing leaks with a DPC falls within the variation of the individual photometer tested in this study. The results provide validity to utilizing low PAO concentrations and DPCs to determine leak size in ePTFE filters. Utilizing this methodology, the loading of the filter will take 150 to 300 times as long based on previous testing. This now provides a method in which the benefits of ePTFE can be utilized in critical pharmaceutical applications.

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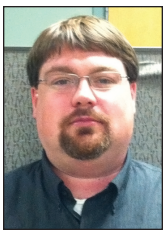

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Understanding Operational Waste from a Lean Biopharmaceutical Perspective

by Richard Benson and Niranjan S. Kulkarni

This article presents different types of operational wastes (non-value adding activities), provides examples of wastes common to pharmaceutical and biotech manufacturing, and lists commonly used techniques to analyze and reduce waste.

Introduction

Companies of all sizes are vying to increase their market share and profitability in a world of shrinking margins, patent expirations, and R&D pipelines that are dwindling. Factors such as increased regulatory requirements and outsourcing increase the need to provide quality products at reduced cost. The problem may be further exacerbated by facility or equipment capacity constraints and limited available capital. Many pharmaceutical companies are now realizing that they can leverage cost saving techniques and models used by the automotive, electronics, and semiconductor industries. These industries pioneered Lean techniques and Six Sigma methodologies, having used them extensively to eliminate waste and variability within their processes. Pharmaceutical companies are now adopting these methods to drive toward improved quality at reduced Cost of Goods Sold (COGS).

The most effective way to reduce costs while keeping up with the competition is to become *"Lean"* by reducing, and preferably eliminating, waste (also referred to as *muda* – Japanese term for waste). Womack and Jones[1] define waste as any activity that does not create value as defined by the ultimate customer. They state that even a casual evaluation/observation of a process will reveal wasteful activities and processes. In the world of Lean, every activity is differentiated as either a Value Adding (VA) or Non-Value Adding (NVA) activity. However, it should be noted that even some perceived NVA activities may be necessary to comply with certain standards and/or regulatory requirements. Such activities are termed as Essential Non-Value Adding (ENVA) activities. Figure 1 illustrates the different categories of activities.

Pharmaceutical and biotech companies need to comply with current Good Manufacturing Practices (cGMPs), GLPs, and GEPs as documented in CFR, Eudralex, and other Rules, Regulations and consensus guidance documents established by the jurisdictional governing bodies, such as the FDA, EMA, WHO, CDSCO, etc. A level of quality that mitigates risk of potential harm to the patient is required. Consistent and validated processing is maintained and constantly verified by applying regulations and by documenting activities critical to product quality. Companies invest heavily in Quality Teams and Systems in order to comply with these requirements. Activities such as internal quality au-

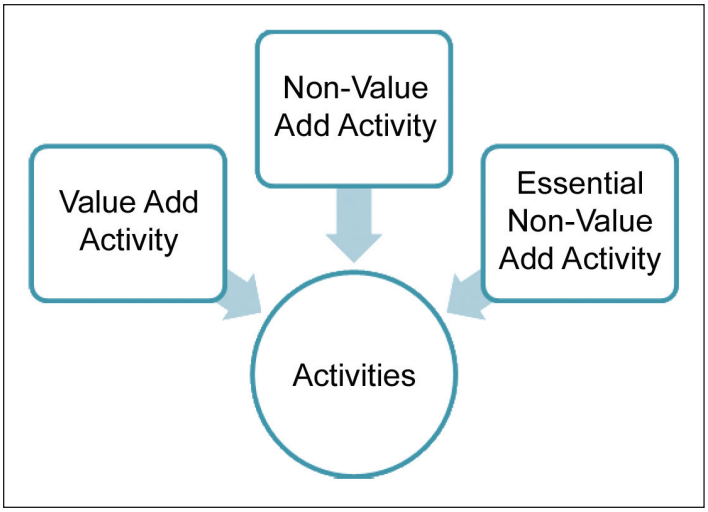

Figure 1. Categorization of activities.

dits, documentation, reviews, etc., have an impact over product quality, and are considered essential activities. However, these activities are put in place to ensure that the VA steps have been properly executed and that no additional costs will be incurred later from recalls or rejects. These activities, by themselves, do not increase the value of the product, they only ensure the product meets specifications; hence, can be termed as ENVA activities.

Furthermore, activities like signoffs, approvals, etc., may be required to meet company or regulatory policies, thus essential to the process. Though such activities are very important from both a traceability and accountability perspective, they can be termed NVA because the customer is not willing to pay extra for it. Consequently, such activities do not directly contribute to the manufacturer's profits and are considered ENVA activities.

Lean techniques are aimed at identifying and eliminating NVA activities. These techniques also should be used to minimize or optimize ENVA activities where possible. Eliminating or reducing the time spent on these wasteful activities can decrease cycle time and improve overall flexibility of the facility. While process and technological changes can help reduce the cycle time of VA activities, these changes also can improve (reduce/eliminate) NVA and ENVA activities.

When analyzing processes and mapping the value stream, it is important to understand exactly what the customer is willing to pay for, i.e., value from the end user's perspective. Anything the customer is unwilling to pay for can be termed waste. Waste, in any form, impacts both direct and indirect costs, which contribute to the overall price of the end product. Direct costs include costs associated with damaged or faulty product, product recalls, loss of resale value, etc. Indirect costs can include insurance premiums, damaged reputation, and loss in customer loyalty. All of these have a negative impact on profitability.

This article focuses on identifying and understanding different types of wastes as defined in the Lean literature and provides examples of waste common to pharmaceutical and biotech manufacturing. Several characteristics of waste are specified that apply to all industries, including biopharmaceuticals, and some of the commonly used tools/techniques used to analyze and reduce wastes are delineated. Waste analysis and reduction techniques and tools can vary depending on the type of waste encountered, the stage in product life cycle, type of facility, etc. Consequently, providing details or examples of waste elimination for such different instances is not included within the scope of the article.

Types of Wastes in Lean

Lean manufacturing focuses on eliminating waste from the process. Taiichi Ohno, the former Toyota executive, suggested that waste accounts for up to 95 percent of all costs in non-Lean environments.[2] He is credited for identifying and formalizing the first seven types of waste. More recently Womack, and Jones[1] appended the list to include an eighth category. Table A lists the eight types of lean wastes. The waste types are further discussed below.

Defects

Defects are the most common form of waste and can be identified easily as damaged goods or non-compliant product. Defects can be found anywhere from the manufacturing process to the analytical lab, and even in the supply chains. In a warehouse, damaged boxes from careless maneuvering can impact raw materials or finished goods, which then need to be repaired or discarded. If a shipping form is not filled out correctly (defect), it can cause delays in the manufacturing process, which in turn delays the shipment of finished goods to the customers. Other documentation errors that can cause delays in the process or additional corrective action are considered waste because they do not add any value to the final product.

Low yield is a good indicator of high levels of defects. In an Oral Solid Dosage (OSD) manufacturing facility, a defect could be a broken tablet, or a label that does not adhere to the bottle it is attached to. Products that do not pass quality inspection are considered defective. In a cell culture process, a non-conforming batch of buffer or harvest contamination are examples of defects.

Many defects can be attributed to variability within a process. According to Dr. Walter Shewhart, there are two types of variability: assignable cause, which represents the randomness of a system outside the process, and chance cause, which is the variability inherent in a process.[3] Lean techniques are used to eliminate assignable cause variation and bring the process into a state of statistical control where it operates within one to three sigma range. Six Sigma tools and methodologies can then be used to reduce variability and eliminate the chance cause to bring the process capability from three to six sigma. The result is a highly controlled process that produces fewer defects, costs less to operate, and allows for any Out of Spec (OOS) product to be easily identified.

Anytime a product is discarded, it directly influences profitability. Furthermore, profitability is also impacted by the stage at which this product is discarded. In a tightly controlled

Waste Type	Description
Defects	Product, service or documentation imperfections, nonconformance, or errors
Inventory	Material supply in excess of that required to meet customer demands
Over-Processing	Additional and unnecessary NVA operations or processes
Waiting	Unproductive time caused due to unavailability of material/resources
Transportation	Movement of materials or people that does not add value
Motion	Unnecessary movement resulting in delays or inefficiencies
Overproduction	Producing more, earlier and faster than the customer demands
Non-utilized talent	Not using people to the best of their abilities

Table A. Lean wastes.

Lean process, defective product will be identified before any further NVA processing can be done on the non-compliant item. In such a scenario, no extra work is performed on a batch or drug container that is already OOS and is destined to be disposed of. This frees up resources downstream to continue processing "good" product, and eliminates further wasteful activities. The processing of OOS product is also known as "over-processing" (described below). However, it is very important to identify the underlying causes resulting in OOS products. Failure Mode and Effects Analysis (FMEA) is one of the commonly used technique for identifying root causes, analyzing the impact of failures, and prioritizing the failure modes. Control procedures should be designed and developed around processes susceptible to creating OOS products to avoid recurrence of such instances.

The costs associated with defective product or materials are primarily direct costs due to lost sales. Additionally, there can be indirect costs associated with defects such as, but not limited to, disposal costs, contamination of process streams, need for additional testing, cleaning, and sanitization. Such costs, especially disposal costs, can be very high when dealing with active pharmaceutical ingredients that may need to be stored securely and incinerated. Although it may be possible to reprocess some products, additional costs will be incurred. As an example, the refiltering of a buffer solution, where the post filter integrity test failed, may be allowed, but the net COGs would need to include the additional components, utilities, and labor required to reprocess the solution. The system integrity failure could also require additional future testing and revalidation of the process, which consume additional resources.

In order to minimize defects and associated costs, the process should be highly robust and repeatable, such that any OOS product is identified immediately. Line tours and process observations can provide good information and insight into the causes leading to defective products. Statistical techniques like Pareto Analysis can be used to identify those processes, equipment, or procedures which cause the highest number of defective (or OOS) products. Data mining techniques and Analysis of Variation (ANOVA) can be used to understand relationships between various factors that generate defects and help to determine the root causes.

Inventory

Inventory is often described as a necessary evil. Inventory consists of raw materials in a warehouse or on a shelf and finished goods. Low inventory (of raw materials) risks starving the process, while holding too much inventory can increase product lead times and warehouse space requirements. It may be difficult to strike the right balance of inventory requirements without advanced data processing or simulation.

Excessive inventory of product is a result of over-production, another type of Lean waste. A study conducted by Schonberger showed that pharmaceutical companies typically carry relatively huge inventories when compared to those of other industries.[4] Many companies use excess inventory to cover variability in the process or uncertainty in demand.

In a truly Lean process, there is no built up Work In Process (WIP) or excess inventory. The process should include one-piece flow of product from one processing step to the next based entirely on customer pull. Raw materials arrive from the supplier only when they are needed. Finished goods are sent directly to the customer once the process is complete. This is very difficult to achieve in highly regulated industries such as biopharmaceutical manufacturing. However, a detailed study of material levels and root causes of variability can help lower excess inventory. Discrete Event Simulation has often been used to model the resource requirements of a process or facility in order to quantify optimal inventory levels.

There are numerous costs associated with inventory. Storing raw materials prior to use requires that you have a warehouse or some type of storage facility, which includes land and construction costs. Furthermore, the materials may require tightly controlled environmental conditions adding to both the installation and operating costs. A company also must track every item that is held in inventory. The material management/tracking systems used for such purposes can become expensive as a result of increased complexity and tracking requirements. In addition, operators are required to receive, inspect, and move materials – another cost factor. There are several risks and costs associated with holding excess inventory, such as damage to raw material, due to unforeseen events, material expirations, products becoming obsolete rendering the material unusable, and contamination to name a few.

Over-Processing

Over-processing is the performance of operations beyond a set (or expected) quality level. If product or processes not only satisfies, but exceeds Critical-To-Quality (CTQ) and/or regulatory requirements (i.e., quality higher than a customer is willing to pay for), it can be described as over-processing. It also includes continuing to process an incorrect product. Such instances can occur if appropriate quality checks are not put in place. Processing or producing at rates exceeding requirements is also a form of over-processing waste.

Quality control falls under this very broad category. A certain level of inspection is required to ensure quality and to meet regulatory expectations. Over-testing has high costs associated with it. At the other extreme, under-testing presents significant risk. Guidelines on minimum sample and quality testing requirements are provided by the Regulatory Agencies to mitigate risks associated with inadequate sampling and testing. Biopharmaceutical companies have always struggled with this balance. Statistical methods such as Six Sigma and sampling plans can be used to determine the appropriate level of quality inspection, sampling, and testing required to comply while minimizing costs. Formal risk assessments will define the areas of highest risk, thereby providing manufacturers a roadmap on where to focus their testing.

Similarly, excessive documentation is another activity that can be considered over-processing waste. CTQ parameters must be monitored during batch processing and recorded

"…time spent waiting for the QA personnel to begin inspection contributed up to 42 percent of the overall cycle time."

in batch records. Today's technology allows for much of this data logging to be performed automatically with any real time deviation or OOS event to be identified immediately, alarming the manufacturer and preventing subsequent manufacture of OOS product. The traditional development and maintenance of batch records can be very inefficient when non-critical information is recorded and further confirmed by secondary signatures. Time lost by operators, approvers, and/or managers on NVA activities, such as documenting unnecessary data or duplicating data, further increases the product COGs. Increased documentation or human involvement also increases the chance of making an error. Sometimes approvals cannot be avoided, but the fewer that are required, the lower are the costs and risks. Electronic Batch Records (EBR) can help overcome some of the problems associated with manual batch records. However, EBRs should be designed to capture the key artifacts and avoid any unnecessary inputs or information.

Over-processing not only increases the overall cycle time, but also affects inventory levels. Many times companies over-process as a precautionary measure. Examples of over-processing include using intensive CIP, SIP, or cleaning regimen when lower grade cleaning/rinse may be adequate, repeating test sequences in commissioning and qualification, performing "pre-validation" activities that are non value added, processing closed unit operations in highly classified cleanroom environments, requiring protocol/record approval signatures of personnel or departments that cannot add value or are not Subject Matter Experts (SMEs), etc. While these activities may be necessary to some extent, they are all examples of over-processing and result in loss of material, manpower, or money in one way or another.

Waiting

Waiting is time wasted waiting to proceed with value added activities. Delays can result from a number of factors. Waiting for release of material or unavailability of QA/QC personnel for verifications/validations and clearances can be a large contributor to increased waiting. In one recent study (confidential client) conducted by the authors, it was observed that time spent waiting for the QA personnel to begin inspection contributed up to 42 percent of the overall cycle time. This waiting time could have been easily eliminated by proper scheduling of activities to ensure that the QA person is not required in more than one place at the same time.

Unavailability of raw materials is another contributor to increased waiting time. This factor is greatly influenced by demand forecasts, reordering strategies, variability in the supply chain, environmental factors, etc. A common strategy is to order surpluses of raw materials to mitigate the risk of shortages and delays. This increases raw material inventories that occupy valuable real estate in the warehouse. As mentioned earlier, a lean operation will only carry the inventory necessary to ensure the customer is satisfied and demand is met.

Improper planning and scheduling also contribute to delays. Variability in upstream processes will impact processes downstream. Delays in the upstream process significantly increase waiting time in the downstream process. Unavailability of equipment (processing or transport) also can add to the waiting time, e.g., unavailability of clean or sterile equipment, assemblies, and kits required for processing, etc. increase waiting time. Equipment idle time adds no value in a lean operation. Bioprocessing equipment has extremely high capital value. Not maximizing its utilization can result in higher product COGs.

Whenever an operator or machine is idle, the company is losing money and other valuable resources. Companies must pay for labor even if an operator was idle (for reasons beyond his/her control) during the shift. In these cases, operators can be reassigned to other tasks. However, if the operators are not trained in these tasks, such reassignments may not be reasonable and add little value to the overall operator utilization.

Transportation and Motion

Excessive movement of raw materials, personnel, or paperwork can be considered NVA activities. Transportation may seem like an essential activity, but a process where every unit operation is physically located adjacent to its upstream and downstream operations does not require transportation. This is often not achievable in biopharm facilities where aseptic processing and environmental cleanroom classifications may require segregation of unit operations and therefore transfer stations and transporters. However, much of the cost associated with transportation and transfer waste can be attributed to inefficient processes and lack of understanding of environmental impact on the operation resulting in poor facility layout design.

Any type of transportation has cost associated with it. Some form of equipment is required, e.g., forklift, hand truck, etc., and these need to be purchased. These equipment items have an initial capital cost, recurring maintenance cost, operator costs, and other indirect costs, such as insurance, training, depreciation, cost to install traffic indicators (overhead traffic signals), etc. Automated Guided Vehicles (AGVs) are viable alternatives to manually operated equipment, but the cost of purchasing, implementing, and validating an automated system may be too high for some companies. For other companies in search of reducing headcount and overhead while

"...waste can be combated by standardizing procedures, ensuring preparedness, efficient layouts, and organized work spaces..."

maximizing the productivity of their work force, automation may be the solution. It should be noted that employing AGVs or automation is justified when tasks are similar in nature, repetitive, and have higher frequency.

Significant transportation waste can be seen if portable equipment and tanks are repeatedly moved around a facility. When a buffer hold bag is transported from a solution prep area to a chromatography suite, the bag holder and operator must pass through air locks. The operator must adorn additional gowning and spend time wiping down the bag holder. Then, once the buffer is consumed, the operator must reverse the process, and spend time de-gowning.

Layouts should be designed such that sequential process steps are adjacent to each other; and material and personnel movement is minimized. Techniques like spaghetti maps or discrete event simulations can be used to analyze the distance traveled by operators in varying layout configurations. Such analysis is especially useful to analyze multi-product facilities or when the operating philosophies are still being defined.

Considerable waste, in terms of time, money, and resources, also can be seen in supply chains. If a distribution center is not optimally located, the overall COGs is higher. Similarly, trucks sent to/from the warehouse without a full load also contribute to transportation wastes as the same amount of time and resources are being consumed regardless of the load.

Motion itself refers to the amount of movement an operator performs. Ideally, an operator could stand still and parts would arrive in order to achieve maximum productivity - again this is not always feasible. Every second an operator has to spend gowning, searching for a flex hose, or even sifting through computer files represents unproductive time and motion that is not spent adding value to the product. This waste can be combated by standardizing procedures, ensuring preparedness, efficient layouts, and organized work spaces, such as those seen when using the 5S5 concept, a Lean housekeeping technique.

Overproduction

Making more than is necessary is a very common practice among biopharm companies. While it may seem logical to keep the shelves stocked and customers instantly gratified, there are some serious risks and costs involved in making more than necessary, such as product expiration, possible contamination from outside sources, deteriorating product quality, etc. Some of these outcomes could have major consequences to the patient and possibly the corporate image. Furthermore, there is also a risk that the product demand could change or a newer/better product is launched by the competition, thus eliminating the demand for the product that has already been made. In such instances, overproduction can lead to significant losses.

The practice of overproduction leads to many other forms of waste, including excess transportation and inventory. Part of the sale price of a product is the cost of distributing and holding of finished goods inventory, but if the product cannot actually be sold, these become sunk costs which hurt profitability. If the product must be disposed of, there is the actual cost of disposal to go along with the loss of the sale.

On a smaller scale, any built up WIP is a result of overproduction from an upstream processing unit. The same risks and costs apply on the process level as they do at an enterprise wide level. As mentioned earlier, in a truly Lean process, there would be one-piece flow with no intermediate inventory and the upstream operation would only produce enough to keep the downstream operation satisfied. This is known as the "next operation as customer" concept by Dr. Kaoru Ishikawa[3] where each downstream operation becomes the customer of the upstream operation.

Demand forecasting and planning are very critical and need to be as accurate as possible in order to reduce overproduction. Furthermore, determining appropriate service levels based on customer needs can prove to be valuable information to address the issue of over-production. It is ideal to create a "pull" environment wherever applicable and feasible. Kanbans can be used to indicate when a downstream operation is ready to receive the next batch. In such instances, the process will commence only after receiving a customer order.

Under-Utilized Talent

Improper utilization of talent and creativity loss is another form of waste that companies should pay close attention to. Examples of this type of waste include selecting an overqualified person to perform a menial task or paying for employee training and then not using his/her skills set.

When planning any modifications to a process, one should always include people who are most familiar with the nuances of a specific process. Managers should take inputs and suggestions from the people who operate the equipment or they run the risk of missing out on very valuable knowledge that comes from working everyday in a specific area/process. This not only gives operators pride in their work, but also ensures that talent and ideas are not lost.

The costs can sometimes be difficult to quantify, but the benefits can be prodigious. Assessing talent is not an easy task, but there are multiple ways a company can maximize the talent they already have and ultimately make more with less. Cross training can help lower overhead (salary, insurance,

"Overcoming the initial hurdle of admitting a process is not perfect can be the hardest part."

gowning, and pension/401k) and maximize productivity.

Characteristics of Waste

Though wastes differ by products, processes, facilities, etc., there are some common traits that are observed:

- Waste, irrespective of type, negatively impacts productivity, flexibility, and profitability.
- Waste will not be always "visible." Obvious waste is easy to reduce/eliminate. However, it is the unseen waste that poses the real threat. This type of waste needs to be identified and eliminated.
- Waste can be concealed even in the (so-called) value added activities.
- Wastes are not always independent of each other. One type of waste can lead to another, e.g., overproduction could increase chances of defects, increase inventory, transportation, etc.
- Some NVA activities are mis-categorized as ENVA activities. Some are due to legacy practices no longer applicable with the use of new technologies and better process understanding. Proper identification of Critical Quality Attributes will lead to a lean Quality Program based on risk to patient.

Tools and Techniques Used in Waste Reduction Efforts

Using the right tools and techniques can help identify, and subsequently reduce (or eliminate), waste from the process. Selection of an appropriate tool/technique is dependent on the problem at hand. Numerous tools and techniques can be employed for the aforementioned purpose. However, we will restrict the discussion to some of the popular techniques used for waste reduction.

A common and most popular lean technique to identify waste is Value Stream Mapping (VSM). A value stream map is more than a flow chart. Using unique symbols, it shows both information and material flow, while capturing VA and NVA activities and their respective durations. This tool is used not only to depict current process, but also can be used to create a vision of future state processes. However, VSM does not capture the impact of variability on a process. Also, it cannot be used to understand the dynamic interactions that occur within the process.

Modeling and simulation can be used to address such shortcomings. Discrete Event Simulations (DES) are very effective in handling variability and interactions. The ability to model random (stochastic) events, e.g., equipment failures, unavailability of resources, unexpected changes in demand, etc., allows DES to mimic the real world operations. DES are often employed to study "what-if" scenarios and to optimize a process or facility. Numerous commercial simulation software are now available, including Flexsim, ProModel, Arena, etc.

Workplace organization using visual techniques also are recommended to reduce waste. Markings, colors, and other visual controls can be used to eliminate excess motion or inventory. Techniques such as 5S, visual production control, e.g, Kanban, and visual information and performance measurement techniques should be employed. Replacing manual operations with automated operations, wherever feasible, will reduce the errors caused by human intervention.

Standardizing equipment, practice, and procedures can significantly reduce wastes. In many instances, standardization improves overall flexibility. Statistical and quality techniques, such as Design of Experiments (DOE), control charts, sampling plans, etc., can be effectively used to reduce waste in a process and even within supply chains.

Conclusions

As pressure to cut costs continues to grow, companies need to reflect on their current practices and identify any possible sources of waste. Lean and Six Sigma methodologies can be used to help identify non value adding activities and eliminate the causes of waste, along with variability in supply, demand, or processing.

Overcoming the initial hurdle of admitting a process is not perfect can be the hardest part. There is a perceived high cost to re-validate a process. Many times, the benefits gained from process improvements can overcome the cost of re-validation within the first year. The savings can be realized as increased capacity or reduced inventory in a warehouse. The benefits are not limited to cost savings, but may include quality improvements and increased flexibility.

When one takes a step back and looks at the process from a different perspective, many forms of waste and unnecessary costs can be seen. A company striving for manufacturing excellence must identify their customer and determine what is absolutely necessary to manufacture the product the end users desire. Once this is done and the waste has been removed, a company can start to see the true variation built into their process and begin to control it using Six Sigma methods. Only then can a process be truly Lean and profits can be maximized.

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This article provides an overview of an ISPE Cleaning Guide currently under development. The Guide will provide a framework for a scientific, risk-based approach to cleaning processes and validation.

Cleaning Validation for the 21st Century: Overview of New ISPE Cleaning Guide

by Andrew Walsh

Introduction

ISPE and representatives from the pharmaceutical industry have entered into a partnership to jointly develop a science- and risk-based approach for the prevention of cross contamination that will, on a case-by-case basis, determine the scope and degree of cleaning validation.

This new ISPE Guide, "Science and Risk-Based Cleaning Process Development and Validation," will describe how to implement cleaning programs, using science- and risk-based approaches, in accordance with the new principles promulgated in ICH Q7 to Q10,[1] FDA's cGMPs for the 21st Century,[2] FDA's PAT Initiative,[3] FDA's Process Validation Guideline,[4] as well as the statistical approaches of "Six Sigma" and "Operational Excellence." The Guide will also describe how to implement cleaning programs that maintain compliance with FDA, EMEA, and MHLW regulatory expectations. A global team of cleaning, cleaning validation, quality assurance, toxicologists, and Six Sigma professionals representing API, clinical, pharmaceutical, and biological manufacturing, as well as FDA representatives has been assembled to develop this Guide.

Background

Cleaning validation is a required activity within the pharmaceutical, biological, nutritional supplement, and medical device industries. From both a regulatory and industry standpoint, cleaning validation is recognized as an important activity to establish that product cross contamination is controlled to ensure patient safety and product quality.

Cleaning validation is an ongoing activity within these cGxP compliant environments which necessitates the investment of significant resources and time. From a simple project management analysis, the time that would be required to perform cleaning validation runs for a non-dedicated facility with multiple products, pieces of equipment, and cleaning procedures can easily run into years. Considering that cleaning runs cannot be scheduled and performed every day and the need for supporting activities including method development, protocol development, laboratory analysis time, and report writing, cleaning validation can consume considerable time and resources.

Companies have made various efforts to reduce the amount of time and resources, such as dedicating equipment or converting to disposable items. These strategies have other inefficiencies and costs associated with them. Even with such efforts, part of the reality has been that, for all intents and purposes, cleaning validation never seems to be completed. This emphasizes that a useful, effective, and efficient cleaning program cannot be developed without focusing efforts and resources where they provide the most value.

With appropriate cleaning development and risk assessments in place, a streamlined cleaning program may be readily developed that is both science-based and risk-based while ensuring patient safety and product quality.

Pharmaceutical manufacturing is in a dramatically revolutionary time in its history. There have been many new, and for this highly conservative industry, radical movements over the past few years from both regulators and within the industry itself. Examples coming from the FDA include "GMPs for the 21st Century," "Quality by Design" (QbD), "Process Analytical Technology" (PAT), and the new Guideline on

Process Validation. Globally, the new ICH guidelines, in particular Q7a to Q10, are another major force driving change in the industry. Movements within manufacturing itself include "Lean Manufacturing," "Six Sigma," and "Operational Excellence" (OpEx) that have grown out of the pressures to reduce costs and to better supply the market. Currently, all these "planets" are aligning to create a tide drawing the industry in a new direction toward science-based, risk-based, and cost effective approaches to ensuring patient safety and product quality during pharmaceutical development and manufacturing. As a critical manufacturing process, cleaning and its validation can benefit from all of these initiatives.

Cleaning, as with many things, has tended to be understood by the industry only in its relation to regulatory expectations. In particular, cleaning has become closely associated with "process validation." In the late 80s/early 90s, the FDA, as well as other regulatory agencies, began to view cleaning as a process and as such, needed to be "validated" similar to process validation. At the same time, several legal decisions concerning cleaning were made during the resolution of the well known Barr Labs case that solidified this viewpoint. Consequently, a great deal of energy began to focus on the "validation" of cleaning procedures, but unfortunately not on the process of cleaning itself.

In many cases, companies set about "validating" cleaning procedures as they existed without questioning whether they were the most effective or optimal, or even if they were using an appropriate cleaning agent. The cleaning procedures that were subsequently "validated" may not have been the best choice for their situation.

Cleaning validation took the traditional pre-approved protocol and three runs "process validation" approach. Because of the traditional "process validation" approach, the industry also struggled over how to set the required "predetermined acceptance limits." Process validation was measured against predetermined specifications. This invoked the question: "What should the "predetermined acceptance criteria" for cleaning be?" This "process validation" approach was adopted without ever asking if three cleaning validation runs were appropriate or were predetermined acceptance criteria appropriate for cleaning validation or verification. Perhaps cleaning, which is considered a process, should be looked at and evaluated differently as is being suggested in the FDA's new Process Validation Guideline.

This ISPE Guide will provide a new approach to meeting regulatory expectations for cleaning and offer a fresh perspective on approaches to cleaning and its validation based on science and risk.

Regulations and the Application of Current Guidance to Cleaning

The cleaning of manufacturing equipment, as a means to prevent cross contamination of pharmaceutical products, is a fundamental aspect of cGMPs. Cleaning, in and of itself, is a relatively simple process; yet, under the pressures of inspectional scrutiny and the reactionary programs created by industry to address regulatory concerns, the validation of cleaning has transformed into a complex, expensive, and time consuming activity. However, all of the industry forces mentioned above offer ways of making sensible changes in the areas of cleaning that would reduce the complexity, lower costs, and shorten the process while providing a high degree of assurance that cleaning has been effective. Before discussing how cleaning and its validation can be changed and improved, the goals of the regulations themselves and the Guidance should be examined.

Code of Federal Regulations

The requirements in 21 CFR 211.67(a)[5] state that:

> *"Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."*

Similarly, 21 CFR 111.27(d)[6] states:

> *"You must maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements."*

21 CFR 820.70(e)[7] also states:

> *"Contamination control. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality."*

From these statements several required elements of a cleaning program can be determined; the scope of cleaning, a required schedule for maintenance, and targets to achieve. To alter the "identity," "strength," or "purity" of a product, gross contamination would be required. Such high levels should not be found after cleaning. However, in some cases, process residues below the order of gross contamination may still affect patient safety and product quality. So one goal of a cleaning program is to verify that no gross contamination remains after cleaning and any process residues do not jeopardize the "safety" of the patient or "quality" of the next product.

ICH Q9 Guidance

Looking at the ICH Q9 guidance, it states two primary principles of quality risk management:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately, link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

By applying these principles to cleaning, it is apparent that cleaning processes should have a risk assessment performed, using science, in the evaluation of the risks the cleaning processes may present to patient safety and product quality. The degree of any activities, such as cleaning development, cleaning validation, cleaning verification, monitoring, etc., should be driven by the level of risk presented. A precedent has already been set for this in the ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP).[8]

cGMPs for the 21st Century Guidance

In the FDA guidance "Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach," there are four principles with particular relevance to cleaning:

- Encourage the early adoption of new technological advances by the pharmaceutical industry.
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches to all aspects of pharmaceutical production and quality assurance.
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas.
- Ensure that regulatory review, compliance, and inspection policies are based on state-of the-art pharmaceutical science.

Applying these principles to cleaning, the degree of any activities, such as cleaning development and cleaning validation, should be driven by the level of risk presented, and in addition, that the use of modern technology to implement these risk-based approaches is to be encouraged.

PAT Guidance

The FDA guidance "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" states:

- A desired goal of the PAT framework is to design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.
- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.

In the PAT guidance, cleaning as a process, should be designed, developed, and well understood, and the use of on-, in-, and/or at-line measurements and controls is encouraged.

Quality by Design

Although the Quality by Design initiative as described in the ICH Q8-Annex addresses product manufacturing processes, there are principles there that can be applied to cleaning processes as well, such as:

- Selecting an appropriate process.
- Identifying a Control Strategy (CS).
- A systematic evaluation, understanding, and refining of the process, including:
  - Identifying, through prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product Critical Quality Attributes (CQAs);
  - Determining the functional relationships that link material attributes and process parameters to product CQAs.
- Using enhanced process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for design space(s) and/or real-time release.

In terms of cleaning, using a systematic approach, such as those described in the ICH Q8-Annex, could enable continual improvement and innovation of cleaning processes without being locked into previously validated parameters and restricted by onerous change control procedures.

Process Validation: General Principles and Practices

The new Guide is intended to align process validation with the product lifecycle concept and with existing FDA guidance on ICH Q8-Q10 and also describe concepts that are directly applicable to cleaning and cleaning validation and the direction of this Guideline.

- Cleaning Process Design – Building and Capturing Process Knowledge and Understanding
  - Application of Design of Experiment
  - Multifactorial Interactions
  - Using Risk Analysis Tools to screen potential variables
- Cleaning Process Qualification
  - Use of statistical methods in analyzing all collected data
- Continued Cleaning Process Verification
  - Use of Statistical Process Control techniques
- Continuous Improvement
  - Use of historical data (monitoring, etc.) or technological advances for improvement of cleaning processes

The elements of the new Process Validation Guideline provide a framework that closely matches the elements of this science- and risk-based guideline.

Operational Excellence and Six Sigma

Operational excellence can be defined as conducting business in a manner that satisfies customer demand, improves quality, and generates higher yields, faster throughput, and less waste. Six Sigma can be defined as a disciplined, data-driven approach and methodology for eliminating defects in

any process.

These two approaches provide statistical tools to improve processes and increase quality. Since cleaning is a process that can be measured, these techniques can be effectively used to improve the cleaning process and enhance the safety and quality of pharmaceutical products.

Goals of Cleaning Based on Current Guidance

By compiling all the elements from the guidance and definitions above into a set of principles, a future vision of cleaning can be derived. This vision is comprised of five main themes: Science, Risk, Design, Validation, and Control. The goals for this Guide are as follows:

Science

An appropriate cleaning program should be based on state-of-the-art pharmaceutical science and design and develop well understood cleaning processes that will consistently ensure a predefined quality at the end of the cleaning process. Scientific knowledge and principles should be considered when defining a cleaning program including, but are not limited to:

- Develop process understanding.
- Identify, define, analyze, evaluate, control, and manage sources of variation - the sources of risk.
- Define, design, develop, optimize, control, and verify cleaning processes and cleaning assessment methodologies.
- Design and implementation of process analytical technologies.
- Describe, analyze, process, interpret, and evaluate information and data obtained from cleaning development and validation studies.

Risk

The cleaning process should have an evaluation of the risk to product quality based on scientific knowledge that focuses both industry and Agency attention on critical areas and ultimately links to patient safety and product quality. The level of risk presented by a cleaning process can be evaluated by considering the various factors associated with cleaning. Questions such as:

- What are the hazards associated with the process residues?
- Are there hazards associated with the cleaning process?
- How hard is it to clean the process residues?
- How effective is the cleaning process?
- Is it hard to detect process residue(s)?
- Can I see process residues below the safe limits?
- Can I visually inspect all of the equipment surfaces?

Based on the answers to these types of questions, the cleaning process can be assigned a position on the scale shown in Figure 1.

Design

For achieving the intended purpose(s) and desired quality objective(s) of cleaning processes, the cleaning processes and related activities shall be designed using scientific knowledge and principles. Such cleaning processes would be consistent with the basic tenet of "Quality by Design" and could reduce risks to patient safety, product quality, and regulatory concerns while improving efficiency. This should include a systematic evaluation, understanding, and refinement of the cleaning processes, including:

- identifying, through prior knowledge, experimentation, and risk assessment, the material attributes and cleaning process parameters (e.g., cleaning agents, product cleanability, raw materials, degradants, time, temperature, etc.) that can have an effect on cleaning Critical Quality Attributes
- determining the functional relationships that link material attributes and cleaning process parameters to cleaning CQAs through understanding of cleaning operating space and design space (e.g., Designed Experiments)
- using science and cleaning process knowledge and understanding for continual improvement of cleaning processes

Validation

Validation in this Guide includes validation and verification activities to ensure a capable cleaning process. Based on the level of risk, stage of development, or level of product understanding, cleaning processes should be subject to scaling levels of validation or verification with greater focus on products and/or processes that present higher risks. For example, cleaning processes for products that present little risk may be validated or verified using visual inspection alone. Also, for example, early stage products may involve higher levels of verification until increased product understanding indicates a low level of risk and a lower level of verification necessary.

Control

An appropriate control strategy should be established. This may include enhanced process understanding and adoption of new technologies in combination with quality risk management. An appropriate strategy may include real-time release of clean equipment using visual inspection, PAT, or real time modeling using multivariate analysis.

Application of Risk and Science to Cleaning

Cleaning Risk Assessment

The subject of "risk" in pharmaceutical manufacturing has

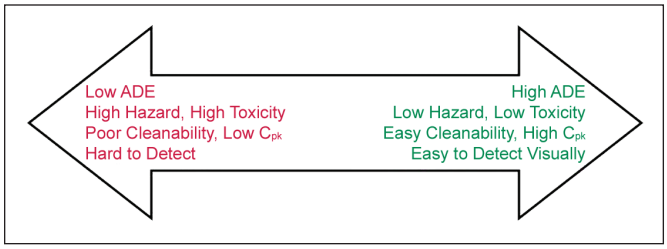

Figure 1. Acceptable Daily Exposure (ADE).

been discussed in ICH Q9 and ISPE's Risk-MaPP Baseline Guide. Risk can be defined as:

Risk = f (Hazard, Exposure)

where Risk is a function of the severity of a hazard and the level of exposure to that hazard.

For the purposes of cleaning, risk can be further defined as:

Risk = f (Hazard, Exposure, Detectability)
or
Risk = f (Severity of Process Residues, Level of Process Residues, Detectability of Process Residues)

For a reliable assessment of risk, it is imperative to have a scientific means (e.g., risk management tools) to identify the hazard presented by a product (e.g, API, degradants, intermediates), cleaning agent or bioburden/endotoxin, evaluate the ability of a cleaning process to remove process residues to levels that are acceptable and the ability to detect and quantify the presence of process residues after cleaning.

Risk analysis may be used to create a scientific rationale for cleaning validation. An evaluation of which process residues should be tested for is based on risk. Based on the level of risk, cleaning processes should be subject to scaling levels of validation or verification with greater focus on processes with higher risks. The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk posed by the cleaning process.

Cleaning Hazard Analysis

The FDA's "Guide to Inspections Validation of Cleaning Processes" under the section on Acceptance Limits states, "The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable." Therefore, limits should be determined that are directly derived from an actual hazard that a process residue may pose.

The hazard presented by a process residue may be determined from a toxicological review performed by an individual(s) qualified to make that assessment, such as a toxicologist. This would involve a thorough review of all relevant toxicological data available for the compound under study. The pharmaceutical industry is unique in that extensive pre-clinical and clinical data on APIs is available to review. When these data are available, an Acceptable Daily Exposure (ADE) can be determined and used as a measure of the severity of hazard presented by the compound. The calculation of an ADE is a standard procedure of toxicology used for decades and is the basis of ISPE's Risk-MaPP Guide. The ADE can be used to calculate a "Maximum Safe Carryover" to evaluate process residue data and determine the level of risk posed by the process residue. When an ADE is not available, such as for intermediates or compounds in early development, alternative approaches such as the "Threshold of Toxicological Concern" may be justified.[9]

The potential hazards presented by equipment design also should be considered. Equipment should be designed to facilitate cleaning, inspection, and monitoring.

Cleaning agents should be selected based on scientific principles and the level of hazard they pose. It is preferable that all cleaning agent components are found on the Generally Recognized As Safe (GRAS) lists. In the case the cleaning agent is not a GRAS material, the ADE can be used to calculate a "Maximum Safe Carryover" to evaluate process residue data and determine the level of risk posed by the process residue.

The hazard of possible bioburden from a previous product and the possibility of microbial proliferation during or after a cleaning process and the hazards this presents needs to be assessed as well. For example, the hazard(s) presented in holding equipment in a dirty state or clean state need to be addressed.

Cleaning Exposure

After the hazard of a compound has been identified and an ADE and corresponding "Maximum Safe Carryover" calculated, steps to minimize and evaluate the levels of possible exposure should be taken.

Prior to use, cleaning procedures should be subjected to risk assessments, e.g., Cleaning Failure Modes and Effects Analysis (FMEA/FMECA) or other risk management tools to minimize risk of failure, improve them, and make them more reliable and robust. If the severity of process residues, level of process residues, and detectability of process residues of the hazard can be measured and quantified, cleaning processes can then be evaluated by risk management tools. Based on the severity posed by process residues, the likelihood of process residues and the ability to detect process residues, a Risk Priority Number (RPN) can be determined for all cleaning process steps. Actions can then be taken to eliminate or reduce the risk of process residues.

Process residue data should be obtained during cleaning process development and statistically analyzed and compared to the "Maximum Safe Carryover" to evaluate the relative risk of cross-contamination. If risks are high, additional measures should be pursued and documented in the cleaning risk assessment. The higher the potential for contamination, the greater the level of effort and degree of documentation required to ensure product quality and patient safety. The lower the potential for contamination, the lower the level of effort and degree of documentation required. If risks cannot be reduced to acceptable levels, the equipment being cleaned should be either dedicated or disposable.

When the Risk Assessment indicates microbial contamination is a concern, such as for sterile equipment, equipment hold times etc., microbial data should be obtained and evaluated to determine what levels of exposure are presented. Microbial data can be evaluated in a manner similar to product residues. A scientifically based technique for evaluation has already been described .[10,11] Where the risk assessment indicates microbial contamination is not a major or critical concern, such as for non-sterile equipment, obtaining microbial data may not be necessary.

Cleaning programs and cleaning master plans should be developed based on the results of hazard analyses and risk assessments.

Cleaning Detection

The ability to detect a hazard when it is present is an important factor in reducing risk. If a hazard can be seen or detected, steps can be immediately taken to remove or reduce the hazard before proceeding to manufacturing.

There are several methods of detecting process residues that are readily applicable to evaluation of cleaning processes and are appropriate for different levels of risk. Methods such as visual inspection, conductivity, total organic carbon analysis, and HPLC are typically used for cleaning validation studies.

Visual inspection is a powerful tool for cleaning validation and verification. Visual inspection allows the detection of contamination concentrated in small areas that could otherwise go undetected by sampling or other analyses. All cleaned accessible surfaces should be evaluated and certified clean through visual inspection. The limit of visual detection can be determined for the process residues of compounds. Visual standards ("coupons") can then be created with specific levels of process residue deposited on them and used to certify inspectors. Extensive work has been done to demonstrate the applicability and validity of visual inspection.[12-17] Visual inspection is most appropriate for products that pose low risks. (Note: Visual inspection may be used with products that pose higher risks if they are easily detected visually.)

Conductivity is another very sensitive tool for detecting the absence or presence of conductive (ionic or charged) compounds and is very useful in determining the presence of most cleaning agents and some products. Conductivity is most often used to determine the completion of Clean-in-Place (CIP) wash cycles. Conductivity is also most appropriate for products that pose low risks, but also can be used with higher risk products if scientifically justified.

Total Organic Carbon (TOC) analysis is another powerful tool for cleaning validation. TOC is a simple and rapid method that can detect low levels of process residues of most pharmaceutical compounds including those considered water-insoluble. TOC is a very easy method to develop and should be the first choice when swab samples are required. TOC is appropriate for cleaning processes that pose low to high risks.

HPLC is a very sensitive tool for detecting process residues and has been extensively used for cleaning validation studies. For process residues, these methods are normally product assay methods converted and validated for trace analysis. HPLC methods are very specific and can only give information on the specific process residue. HPLC should be the choice when methods such as visual inspection and TOC cannot be used. HPLC is most appropriate for cleaning processes that pose high risks that cannot be satisfactorily addressed by the previously described methods.

For validated cleaning processes, monitoring programs should be employed where risks are highest[18] and should be PAT-based if possible. The use of online, inline, or at-line sensors to determine when cleaning is complete is encouraged. Analyses such as visual inspection, TOC, pH, and conductivity may be appropriate in a monitoring program.

Risk Parameter	Hazard	Occurrence	Detectability
Risk Categories	**(Severity)**	**(Exposure)**	**(Detectability)**
Cleaning aspects	- API Residue - Cleaning Agent Residue - Microbial Growth - Degradants	- SOP Risk Assessment - Training Program - Statistical Analysis of Swab Data - Risk Assessment Based on Data	- Visual Inspection - Online Sensors - At-line Sensors - Other Monitoring

Table A.

In summary, for cleaning the parameters of hazard, exposure, and detectability can be mapped as shown in Table A.

Summary

The Guide described above will provide a framework for a scientific, risk-based approach to cleaning of products. The Guide will address how well established and accepted risk assessment methods can be used to develop health-based limits such as ADE and Maximum Safe Carry over (MSC) values.

This Guide will be applicable to the development and validation of cleaning processes for all health, medical, cosmetics, and consumer products, which includes pharmaceuticals (APIs, dosage forms, veterinary, biologics, and clinical supplies), dietary supplements, and medical devices.

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International

US, Russian Health Organizations Pledge Cooperation in Improving Quality of Medicines[1]

Formalizing a mutual commitment to improving the quality of medicines for citizens of the United States and the Russian Federation, officials from the Ministry of Healthcare and Social Development of the Russian Federation and the United States Pharmacopeial Convention (USP) signed a Memorandum of Understanding (MOU). The MOU establishes a mechanism for cooperation between the two groups in a host of areas related to drug quality.

Chinese SFDA Deputy Commissioner Wu Zhen Meets the Head of Iran's Innovation and Technology Cooperation Center[2]

On the morning of 6 September 2011, Wu Zhen, Deputy Commissioner of the State Food and Drug Administration (SFDA), met with the visiting Mr. Hamidreza Amirinia, Head of Innovation and Technology Cooperation Center of Iran. Both parties exchanged views on enhancing mutual exchanges and understanding, and promoting cooperation in the field of traditional Chinese medicine and biopharmaceuticals.

US FDA, International Counterparts Report Progress on Drug Inspection Collaboration[3]

The US Food and Drug Administration, together with its European and Australian counterparts, released two reports detailing the results of pilot programs focused on increasing international regulatory collaboration among the agencies so that drug quality and safety can be enhanced globally.

The report on the Good Clinical Practice (GCP) initiative details the success of information-sharing and collaboration on inspections relating to clinical trials. Under the GCP pilot program, the FDA and the European Medicines Agency (EMA) exchanged more than 250 documents relating to 54 different drug products and, in conjunction with the GCP inspectors of the EU member states, organized 13 collaborative inspections of clinical trials. This lays the foundation for a more efficient use of limited resources, improved inspectional coverage, and better understanding of each agency's inspection procedures. It demonstrates how the agencies can work together to improve human subject protection and better ensure the integrity of data submitted as the basis for drug approvals.

The report on the Active Pharmaceutical Ingredients initiative details the success of information-sharing among the FDA, Australia's Therapeutic Goods Administration and for Europe, the EMA, France, Germany, Ireland, Italy, the United Kingdom and European Directorate for the Quality of Medicines & Healthcare (EDQM). Over the course of the 24 month pilot phase, the participants shared their surveillance lists and found 97 sites common to all three regions, resulting in the exchange of nearly 100 inspection reports and in nine collaborative inspections. The FDA used these reports to inform decisions, such as whether to postpone or expedite its own inspection. The FDA also prohibited imports into the US of a firm's products based on the negative findings from a European inspection. The information-sharing and collaborative inspections were important milestones in establishing a sense of mutual trust and common purpose among the drug regulatory agencies involved.

Asia/Pacific Rim

Australia/New Zealand

Amendments to New Zealand's "Medicines Regulations 1984" Take Effect[4]

The Medicines Amendment Regulations 2011 were gazetted on 14 July 2011 and are available on the Government's Legislation website (www.Legislation.govt.nz). With the exception of those regulations relating to aligning prescribing and the form of a prescription, the changes come into effect on 1 August 2011. The remaining changes will come into effect on 1 December 2011, allowing time for the necessary changes to be made to prescribing software.

India

Indian Ministry of Health and Family Welfare Creates 12 New Drug Advisory Committees[5]

The Indian Ministry of Health and Family Welfare has created new drug advisory committees in the following areas: reproductive/urology; cardiovascular/renal; ophthalmology; vaccines; dermatology/allergies; analgesics/anesthetics/rheumatology; neurology/psychiatry; pulmonary; oncology/hematology; gastroenterology/hepatology; metabolism/endocrinology; and antimicrobial/antiparasitic/antifungal/antiviral.

Japan

Japan Publishes Draft Guidance on Risk Management[6]

This guidance is intended to propose a standard concept for "Pharmacovigilance Plan" and "Risk Minimization Plan" by Marketing Authorization Holders in order to deal with "Important identified risks," " important potential risks" and "important missing information" as shown in Safety Specification in the time of approval review and during the period of post-marketing in accordance with Pharmacovigilance Planning – ICH Harmonised Tripartite Guideline: Notice No. 0916001, from the Director of the Evaluation and Licensing Division and the Director of Safety Division Pharmaceutical and Food Safety Bureau, and Ministry of Health, Labour and Welfare (MHLW), dated 16 September 2005.

Europe

Denmark

Dr. Christian Schneider Joins the Danish Medicines Agency as Senior Medical Officer[7]

As of 1 October 2011, Dr. Christian Schneider filled the position as Senior Medical Officer in the Licensing Division of the Danish Medicines Agency. Dr. Schneider is currently chairman of the Committee for Advanced Therapies (CAT) and the CHMP Similar Biological (Biosimilar) Medicinal Products Working Party (BMWP), as well as co-opted member of the CHMP at the European Medicines Agency (EMA).

Dr. Schneider is a medical doctor trained in medical biochemistry and

clinical immunology from Friedrich-Alexander University, and is a well-known member of several EMA committees and working parties as well as an internationally renowned speaker at scientific meetings. Up until now, he has been Head of Division for EU-Co-operation/Microbiology at the German Paul-Ehrlich Institute.

European Union

EU Releases Concept Paper on Pharmacovigilance Implementing Measures for Consultation[8]

The European Commission is seeking views from the public on a concept paper on implementing measures for the performance of activities related to the safety monitoring of medicines.

The paper, which was open for consultation until 7 November 2011, provides technical details that the European Medicines Agency, medicines regulatory authorities in European Union (EU) Member States, and marketing-authorization holders will need to apply when implementing the new pharmacovigilance legislation.

First Ever Children's Medicine to Hold New Pediatric Use Marketing Authorization Has Been Granted by the European Commission

The first ever children's medicine to hold a new pediatric use marketing authorization (PUMA) has been granted by the European Commission. The medicine, Buccolam, is now specifically licensed for children aged three months to 18 years to treat severe convulsions and epileptic seizures. The news is a landmark in the Medicines and Healthcare products Regulatory Agency's (MHRA's) ongoing campaign to improve the quality, safety, and efficacy of children's medicines available in the UK. The MHRA has been advocating the increased availability of specific children's-only medicines for several years in recognition that many adult medicines are offered to children in cut-down doses.

United Kingdom

Britain Seeks New Members for Drug Advisory Committees[9]

The Commission on Human Medicines (CHM), the Herbal Medicines Advisory Committee and the Advisory Board on the Registration of Homeopathic Products are looking to recruit new members and commissioners. The following positions are available:

- four new members for the Advisory Board on the Registration of Homeopathic Products
- two new members for the Herbal Medicines Advisory Committee
- seven new commissioners for the Commission on Human Medicines

Britain Publishes "Red Tape Challenge: Your Views on Regulatory Enforcement"

The "Red Tape Challenge" is a government initiative to reduce the burden of regulation. It enables the public to comment on government regulations. Every few weeks regulations split into themes affecting one specific sector or industry will be published on the "Red Tape Challenge" website. All these regulations will be open for comments.

North/South America

Canada

Health Canada Proposes to Amend the Food and Drug Regulations with Respect to Radiopharmaceuticals[10]

Health Canada is inviting input in the following areas with regard to radiopharmaceuticals:

- In your opinion, would minor changes in radiopharmaceutical labelling pose any undue burden on your organization?
- Do you have additional comments concerning the regulatory proposal for the use of PERs in basic research studies?

Health Canada to Stop Sending Validation Reports for Passed Submissions[11]

Health Canada uses the LORENZ eValidator™ for the validation of submissions in both the Electronic Common Technical Document (eCTD) and non-eCTD format. It is a standalone application that verifies and validates submissions based on configured check options and verification rules set in accordance to specified Document Type Definitions (DTDs) and various requirements published by the International Conference on Harmonization and other authorities. The result of the validation is a structured report listing the analyzed items.

As of 1 October 2011, Health Canada no longer provides the Validation Reports or email notifications for submissions that have passed validation. Any submissions that have warnings or fails validation will still have a validation report sent to the sponsor.

The Use of Foreign Reviews by Health Canada – Guidance Document[12]

The purpose of this document is to provide guidance to market authorization holders on how Health Canada uses foreign reviews, and how they can help facilitate this use. Recognizing that market authorization holders currently provide foreign reviews to Health Canada, the principles and practices described in this draft document may currently be used, and will serve to formalize the existing practices until such time as the guidance is finalized. This guidance document is applicable to human and veterinary biologics, disinfectants, radiopharmaceuticals and pharmaceuticals, and medical devices.

Health Canada Publishes Inspection Strategy for Medical Device Companies[13]

The purpose of this document is to detail the strategy for the effective and uniform implementation of a national inspection program for the medical device industry in order to assess compliance against applicable requirements of the Food and Drugs Act and the Medical Devices Regulations.

United States

Securing the Pharmaceutical Supply Chain - Congressional Testimony by M. Autor, Esq., US Deputy Commissioner for Global Regulatory Operations and Policy[14]

This testimony advocates modernizing

Concludes on page 96.

FDA's approach to drug safety.

US FDA to Seek Public Comment on IOM Recommendations[15]

The FDA announced that it will open a public docket to begin receiving public comments on the Institute of Medicine's (IOM) report on the 510(k) program, the most common pathway to market for lower-risk medical devices. The FDA commissioned the report in September 2009. While none of the IOM's recommendations are binding, the FDA is planning a public meeting in the coming weeks to discuss recommendations made in the report, titled "Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years."

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Introducing the 2011-2012 Board of Directors

The following pharmaceutical industry professionals have been elected to positions on the 2011-2012 ISPE International Board of Directors:

Officers

Chairman: **Arthur "Randy" Perez, PhD,** Director, IT Risk Management and Compliance, Novartis Pharmaceuticals, USA

Vice Chairman: **Charlotte Enghave Fruergaard, PhD,** Director of Technology, Finished Pharma, NNE Pharmaplan, Denmark

Treasurer: **Damian Greene,** Senior Director, Network Strategy, Pfizer Global Supply, USA

Secretary: **Brian H. Lange, PE,** PMO Operations Director, North American Operations and Merck Consumer Care, Merck & Co., Inc., USA

Re-elected Directors

Doyle R. Johnson, Consultant, former Senior Director, Facilities, Operations, Biologics Division, Genzyme, USA

Morten Stenkilde, Quality Director, Insulin Filling plant, Tianjin, China, Novo Nordisk A/S

New Directors

James A. Breen, Jr., Vice President, Project Management, Johnson & Johnson Worldwide Engineering and Technical Operations Group, USA

Tim Howard, CPIP, PE, Vice President, Company Officer, Commissioning Agents, Inc., USA

Andrew D. Skibo, Executive Vice President, Operations, MedImmune, USA

Udo Vetter, Chairman, Control Board, Vetter Group, Germany

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Joe Famulare, Senior Director, Genentech, Member of the Roche Group, USA

Gordon Leichter, PhD, Regional Sales Manager, Belimed Infection Control, USA

Steve Tyler, Director, Analytics and Technical Projects, Global Pharmaceutical Operations, Abbott Laboratories, USA

Guy Wingate, PhD, Vice President and Compliance Officer, Global Manufacturing and Supply, GlaxoSmithKline, United Kingdom

Past Chairman

Andre Walker, CPIP, Director, Manufacturing Sciences, Manufacturing Operations, Biogen Idec, Denmark

An Expression of Gratitude from the Japan Affiliate

More than a half-year after the Great East Japan earthquake, the effects are still felt throughout Japan. Restoration of the affected region will take decades, and yet, the most precious losses – loved ones, homes, pets and memories – will never be recovered. While Japan is a country accustomed to natural disasters, the calamity of last spring has left an indelible mark, not just on us those for whom Japan is home, but on everyone around the world who holds Japan dear in their hearts.

Recently, we have observed significant milestones in the recovery effort. Owing to the sacrifices made by those of us in the Tokyo region through drastic energy reduction and flexible work schedules, throughout the summer we were not subjected to the rolling blackouts we had feared. Also, recently it was reported that the temperatures of the pools in all the damaged reactors at the Fukushima power plant had dropped below 100°C for the first time, thanks to the heroic efforts of all involved in bringing the situation under control.

We in the pharmaceutical industry have been very busy restoring operations at plants and related industries in the Tohoku region. The progress has been frustrating at times, but on the whole, we are very proud of the combined efforts of contractors, engineers, and suppliers, all of whom have pulled together to get this nation's pharmaceutical supply chain back on track as quickly as possible.

The show of support from the global community has been tremendous. Thanks to the generosity of ISPE Affiliates and Chapters around the world and ISPE HQ, we have been informed that a total donation has been made to the Japanese Red Cross. While we at the ISPE Japan Affiliate have always felt that such generosity and volunteerism are the keys to ISPE's value within the pharmaceutical community, we are humbled by the spirit of giving we have witnessed in recent months. For this, we wish to express on behalf of the Japan Affiliate deep gratitude for the donations made to Japan.

Sincerely,

Tatsuro Miyagawa, Chairman,
on behalf of the ISPE Japan Affiliate

Pharmaceutical Engineering Announces Winner of the Article of the Year Award

Pharmaceutical Engineering's "Article of the Year" recognizes the contribution of authors. Articles are evaluated by a panel of volunteer reviewers according to a number of criteria, concentrating on the importance and timeliness of the subject matter and the quality of the presentation. The criteria for judging are as follows:

- Is it directly useful to the readers in their efforts to improve the industry and themselves?
- Does it improve knowledge/understanding of key topics?
- Is it clear, easy to read? (Low jargon usage)
- Quality of artwork, graphs, etc.
- Appropriate length

The finalists for each "Article of the Year" are chosen from the September/October issue of the previous year, through the July/August issue of the current year. The award program was established to express appreciation to all of the authors who submit their work for publication in *Pharmaceutical Engineering*.

We are pleased to announce the 2010-2011 Roger F. Sherwood Article of the Year Award Winner:

July/August 2011, Volume 31, Number 4

Quality Risk Management (QRM) Tool Selection: Getting to Right First Time

by Kristin S. Murray and Stephen Reich

This article presents how the quality and utility of Quality Risk Management (QRM) may be highly influenced by the selection of risk management tools. Tangible job aids and methods that have been proven to facilitate right-first-time tool selection are presented.

Roger F. Sherwood Article of the Year
PHARMACEUTICAL ENGINEERING®

The winner was selected from this group of finalists and recognized at ISPE's 2011 Annual Meeting.

September/October 2010, Volume 30, Number 5

Lean Maintenance – A Risk-Based Approach

by Gerard Clarke, Gerry Mulryan, and Padraig Liggan

This article presents an industry case study of the application of lean maintenance methodologies carried out at the Pfizer Biotech, Grange Castle Campus, Dublin.

November/December 2010, Volume 30, Number 6

IT Outsourcing and Offshoring: Recognizing and Managing Risk

by Arthur D. Perez, PhD and Glenn Morton

This article discusses risks and mitigation strategies that need to be considered between healthcare companies and outsourced IT suppliers.

January/February 2011, Volume 31, Number 1

Risk Management – A Key Requirement for Project Success

by Brett Schroeder, John Alkemade, and Gordon Lawrence

This article discusses how risk management can aid in project success. It looks at the potential gain from good risk management, examines some typical risks that recur regularly on projects, and offers a suggested methodology for managing project risks.

March/April 2011, Volume 31, Number 2

Business Process Management (BPM) Based Pharmaceutical Quality Management Systems: A Win-Win Between Compliance and Competitiveness

by François Versini

This article shows how a BPM-based Quality Management System optimizes the way to comply with today's evolving processes and stay competitive in the marketplace.

May/June 2011, Volume 31, Number 3

Standardizing Equipment Maintenance Outsourcing

by Martin van den Hout

The article presents points to consider to successfully outsource maintenance activities in a pharmaceutical company.

ISPE Launches New Website

New site structure built to make ISPE technical resources easier to find and access

ISPE launched a complete redesign of its website, www.ISPE.org, in October. The redesign features a reorganization of the site's content as well as an updated look and navigation scheme.

"One of the main ways that ISPE supports our Members in their mission to create safer, less expensive medicines globally is by sourcing and housing a tremendous amount of technical information for their reference," said ISPE President and CEO Bob Best. "I'm pleased to report that the new site is a tremendous improvement over the last iteration, on which content was sometimes difficult to find. This redesigned site was built from the ground up with the goal of making it easier for Members and visitors to find the information they need. The result is a site that is better organized, more intuitive to use, and much fresher in its look."

Under the new website structure, the majority of ISPE's most popular and frequently utilized resources are accessible directly from the homepage, minimizing the number of clicks and amount of time users need to find them. All resources also have been organized according to topic of interest, so that users searching for webinars, education and training offerings, and Guidance documents related to specific disciplines (such as HVAC, commissioning and qualification, or GAMP) will be able to find all available resources on the topic in one place.

This rollout is the first step in a multi-phase project to update and improve the web experience for users of www.ISPE.org. Future phases of the project will contain functionality and performance enhancements as well as the addition of Web 2.0 technologies, such as RSS feeds.

ISPE welcomes feedback on the new ISPE website. Comments can be sent to cmuratore@ispe.org.

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Inhibitory Effect of Silkworm Extract on Alpha-Glucosidase Activity and Postprandial Blood Glucose in Mice

by Juan Cueva, Patricio Castillo, Giovanna Allara-Salice, and Angel Guevara

Introduction

Diabetes mellitus type 2 is a metabolic disorder with high percentages of morbidity and mortality.[1] Due to an asymptomatic pre-diabetic phase, 40% of patients are not aware of their condition until they have reached an advanced stage. However, in some cases, prevention and control of type 2 diabetes is possible with change of habits and/or therapeutic treatment.[1]

Long-term hyperglycemia has a tight relationship with type 2 diabetes development. Thus, patients on a pre-diabetic state have a higher risk to develop this condition and cardiovascular disease.[2] Throughout time, hyperglycemia contributes to insulin resistance; the risk of diabetes increases annually from 3.6 to 8.7% on Impaired Glucose Tolerance (IGT) patients.[3] Similarly, coronary artery disease lipid and non-lipid risk factors are associated with a pre-diabetic state whether a diabetic condition is shown or not in the patient.[4]

1-deoxynojirimycin (DNJ), a poly-hydroxylated alkaloid isolated from mulberry leaves[5] and silkworm,[6] has been found to be a potent inhibitor of intestinal alpha-glycosidases.[5,7] However, there are only few sources of evidence that address the potential of silkworm as a blood glucose-lowering product on diabetic patients;[8,9] moreover, there is limited investigation related to the specific enzyme inhibition mechanism.

In the present study, an ethanol extract from silkworm larvae was prepared and tested *in vitro* for alpha-glucosidase activity inhibition. Furthermore, postprandial antihyperglycemic effect was examined in mice by using oral doses of Silkworm Larvae Extract (SLE). Analysis of the results shows that SLE or other food products derived from silkworm larvae could contribute positively to diabetes mellitus prevention if used as an alternative dietary supplement.

Experimental Procedures

Materials

Alpha-glucosidase (EC 3.2.1.20) from baker's yeast and a Glucose (HK) Assay Kit GAHK-20 were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Maltose monohydrate was purchased from Himedia Laboratories (Mumbai, India). Silkworm larvae were provided by Instituto Agropecuario Superior Andino IASA II (Escuela Politécnica del Ejército, Santo Domingo, Ecuador).

Preparation of Silkworm Larvae Extract

Third-day, fifth-instar *Bombyx mori* larvae were collected on aseptic conditions. An appropriate amount of larvae was homogenized with 4°C water and extracted with 50% ethanol for 72 hours. Then, the extract was filtered and centrifuged to separate from solids. Concentration was performed on a rotavapor at 50°C until a volume of 50% was reduced from the original value. The concentrated extract was then lyophilized (-46°C and 145E-3 mbar for 48 hours) and frozen at -20°C until further use.

Inhibition Assay

Various concentrations of SLE (0.02-14.00 mg/ml) were premixed with maltose solution (50 mM) in phosphate buffer + EDTA (pH 7.0) and incubated at 37°C for five minutes. The reaction was started with the addition of alpha-glucosidase (0.05 mg/ml), carried out at 37°C, and stopped with boiling water. Alpha-glucosidase activity was determined by measuring the

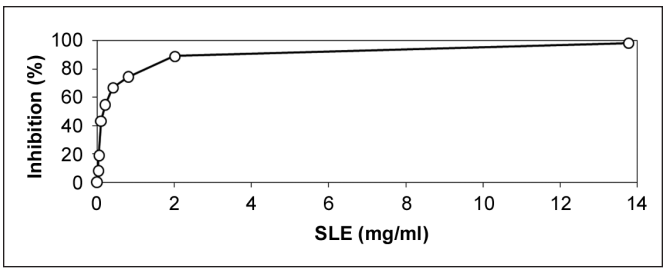

Figure 1. Effect of SLE on baker's yeast alpha-glucosidase activity. A pure inhibition mode was detected with a high SLE concentration when inhibition percentage got a value close to 100%.

concentration of glucose released from maltose with a benchtop spectrophotometer set at a wave length value of 340 nm.

Kinetics of Alpha-Glucosidase Inhibition

Increasing concentrations of maltose substrate (25-500 mM) were assayed in the absence and presence of SLE at two different concentrations (0.1 and 0.2 mg/ml) according to the guidelines established by Murphy *et al*.[10] Kinetic parameters and the inhibition mechanism by SLE on alpha-glucosidase activity were determined by Lineweaver–Burk plot analysis of results. All enzymatic assays were replicated three times.

BALB/c Mice Experiment

Two-month-old male BALB/c mice were purchased from the breeding facilities of Universidad Central del Ecuador (Quito, Ecuador). The animals were acclimated for two weeks with a normal pelletized diet and water *ad libitum*. Twelve hours before experimentation, the mice were deprived of food. On experimentation day, blood glucose concentration values were measured before and after ingestion of several oral treatments (water; maltose solution [2.00 g/kg]; maltose solution + acarbose [0.05 g/kg]; maltose solution + SLE [0.08 g/kg]; maltose solution + SLE [0.40 g/kg]) by using glucometer Accu-Check Active (Roche® Diagnostics, Mannheim, Germany) and by following blood collection procedures described by Hoff.[11] Samples were collected before the oral treatment administration and after 30, 90, 60, and 150 minutes. All assays were replicated five times.

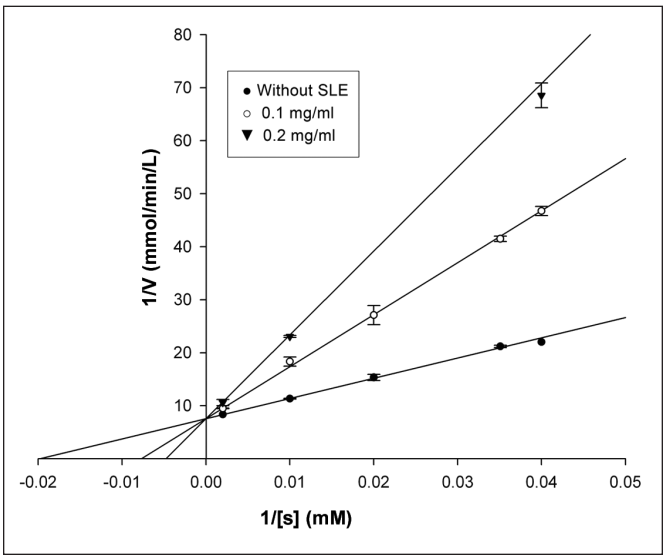

Figure 2. Lineweaver-Burk plot for kinetic analysis of alpha-glucosidase inhibition by SLE. Various concentrations of substrate maltose were assayed at different concentrations of SLE (•, no inhibitor; ○, 0.1 mg/ml; ▼, 0.2 mg/ml). The inhibitory mechanism of the extract of silkworm larvae SLE over alpha-glucosidase activity was competitive.

Statistical Analysis

Statistical significance was evaluated by ANOVA using SPSS v14.0 (SPSS Institute, Cary, NC, USA) and a P-value of < 0.05. Individual comparisons were obtained by Tukey-Kramer's test with an alpha-value of 0.01.

Results

Alpha-Glucosidase Activity Inhibition by SLE

SLE showed to be an effective inhibitor on baker's yeast alpha-glucosidase activity. Figure 1 shows a dose-response curve of inhibition versus SLE concentration. At high SLE concentrations it was possible to reach high inhibition percentages, up to 100% which suggests a pure inhibition mode.

Kinetic Analysis of Inhibition by SLE on Alpha-Glucosidase

The inhibition mechanism of SLE on alpha-glucosidase activity was analyzed by Lineweaver-Burk plots. Competitive inhibition is clearly elucidated in Figure 2, when various concentrations of maltose were assayed at different concentrations of SLE. The Km value of maltose for baker's yeast alpha-glucosidase was 50.50 ± 1.97 mM and the Ki value of SLE was 0.064 ± 0.003 mg/ml (~2.2E-2 mM).

Effect of SLE on Postprandial Blood Glucose in Mice

A suppressive effect of SLE on the increment of blood glucose concentration in mice was observed when it was administered as an oral treatment (Figure 3). Blood glucose concentration of mice after 12 hours of starvation was in the range of 62.2 ± 8.7 mg/dl. When a solution of maltose alone (2 g/kg) was ingested, blood glucose concentrations increased rapidly to values in the range of 183.0 ± 9.6 mg/dl after 30 minutes and decreased thereafter to basal levels. By contrast, when maltose was administered with 0.08 g/kg and 0.40 g/kg of SLE, the increase of blood glucose concentration reduced in 54.9% and 85.1% respectively in a dose-dependant manner. A commercial brand of acarbose was assayed as an enzyme inhibitor as well. When 0.05 g/kg of acarbose was given simultaneously with maltose, the inhibition percentage was 75.9%.

Discussion

SLE showed to be an effective inhibitor on baker's yeast alpha-glucosidase activity. Competitive inhibitors are molecules with analog structures to the respective substrate and bind to the same enzyme's active site.[12] This mechanism of inhibition was expected for SLE according to other investigations using DNJ as an alpha-glucosidase inhibitor.[13-15] Moreover, alpha-glucosidase activity was restrained almost 100% when assayed with high SLE concentrations. This fact indicates that

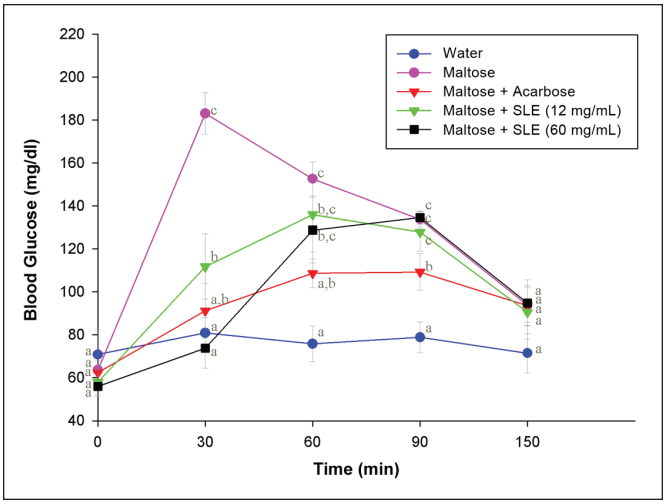

Figure 3. Suppressive effect of silkworm larvae extract on increments in glucose concentration in mice after oral treatments. At time zero, the average value of glucose concentration was in the range of 62.2 ± 8.7 mg/dl. After administration of oral treatments, blood glucose concentrations were significantly affected according to ANOVA and Tukey-Kramer multiple comparison tests. Letters a, b and c differentiate treatments statistically. Results are expressed as mean values ± standard deviation shown by vertical bars (n = 5, P<0.01).

SLE does not form a productive enzyme-substrate-inhibitor complex. Thus, the inhibitor reaction with alpha-glucosidase is a pure competitive inhibition.

Given that alpha-glucosidase reaction with maltose is of low catalytic efficiency (kcat = 3.025 s^{-1}), it is possible to say that the calculated value of Km represents the enzyme affinity for the substrate.[12] A Km value of 4.3 mM was reported when human and rat intestinal mucosas were used as the source of alpha-glucosidase for enzyme kinetics assays.[13] Therefore, mammalian alpha-glucosidase affinity for maltose is about ten times greater than baker's yeast alpha-glucosidase affinity.

A model *in vivo* was necessary to elucidate the effectiveness of SLE as a lowering agent of glucose concentration in mammal blood. Indeed, a suppressive effect of SLE on the increment of blood glucose concentration in mice was observed when administered as an oral treatment. When maltose was administered with 0.08 g/kg and 0.40 g/kg of SLE, the increase of blood glucose concentration reduced in 54.9% and 85.1% respectively in a dose dependant manner, similarly to the results observed for acarbose, with an inhibition percentage of 75.9% when a dose of 0.05 g/kg was used.

Worldwide, more than 171 million people were diagnosed with diabetes with a prevalence of 2.8% and it will almost double for the year 2030. In addition, postprandial hyperglycemia may contribute to the increase in glycosylated hemoglobin blood levels, which leads to the development of the chronic vascular complications associated with diabetes.[16] We strongly believe that functional foods derived from silkworm can help in pre-diabetic stages and could be used as an alternative dietary supplement for diabetes prevention and control.

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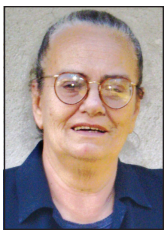

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