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2011 Golf Social

Fun Under the Sun

Golf Chair Beth Meinig along with many volunteers greeted golfers on June 10th at the Lochmere Golf Course located in Cary, NC. Golfers were given a PDA Southeast bag which included goodie items from the many sponsors. As everyone made the turn, there were several opportunities to test your skill. As the chipping contest ended, the winner Michael Sherrill was able to get 18 golf balls in the monogramed PDA Southeast circle provided by the Lochmere Staff. If chipping wasn't your game, then there was putting. Blake Derrick was the winner of the putting challenge.

As for the competitivness on the course, the following individuals and teams took the prizes:

First Place(58)	*Blake Derrick* *David Smith* *Ron Backman* *Glenn Smeal*
Second Place(61)	*Todd Rausch* *Michael Sherrill* *Nate Meyer* *Matt Francis*
Highest Score	*Wyetta Palmby* *Ross Blum* *Susan Schilling*
Closest to the Pin	*Todd Prudent*
Longest Drive	
Women	*Susan Schilling*
Men	*Nate Meyer*

For the photo gallery, please go to page 24

In this issue

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Planning and Executing Cycle Development for the Vapor Hydrogen Peroxide Decontamination of a Filling Line Isolator

1. INTRODUCTION

The cycle development approach described in this document is fairly universal and should not be dependant on individual isolator systems. The terminology used may be slightly different depending on the technology, but the general principles, process descriptions, and process and execution steps can still be applied across various isolator systems.

2. PURPOSE

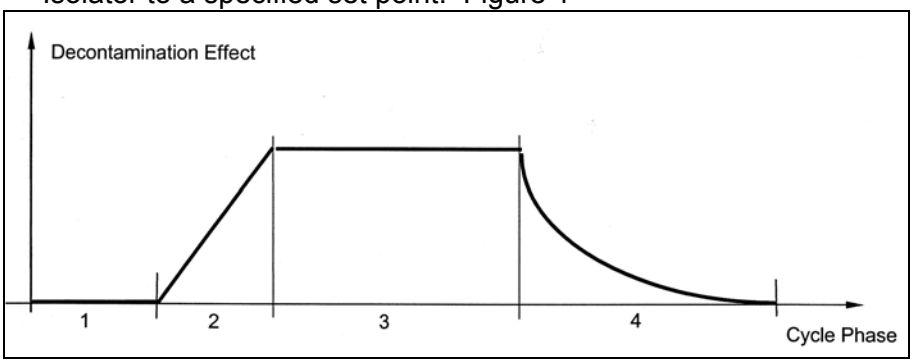
The purpose of this white paper is to provide a High-Level overview and road map to plan and execute of the following aspects of H_2O_2 decontamination cycle development.

- A process overview of the Vapor Hydrogen Peroxide (H_2O_2) decontamination cycle.
- The planning and pre-requisites activities that must be completed prior to the execution of the H_2O_2 decontamination cycle development.
- Execution of the H_2O_2 decontamination cycle development
- Performance Qualification (PQ) of the H_2O_2 decontamination cycle development.

3. H_2O_2 DECONTAMINATION CYCLE PHASES:

The typical decontamination cycle consists of four separate and distinct phases: Pre-Conditioning, Conditioning, Decontamination and Aeration.

1. Pre-Conditioning
    a. The initial physical conditions of temperature, humidity and air velocity inside the isolator are established. Additionally, the vaporizing plates are heated to a set-point temperature and the liquid H_2O_2 is delivered to the vaporizing plates. Typically the control system of the isolator will determine if a sufficient amount of liquid H_2O_2 is available to complete the decontamination cycle. H_2O_2 is not injected into the isolator during this phase. This phase only establishes the proper condition to successfully and repeatedly execute the H_2O_2 decontamination
2. Conditioning
    a. During the conditioning phase, vapor phase hydrogen peroxide is introduced into the isolator chamber and prepares the isolator environment for the desired decontamination effect.
3. Decontamination
    a. Decontamination is the process step where the desired decontamination effect is achieved.
4. Aeration
    a. Aeration is the final process step that removes the residual H_2O_2 from the Isolator to a specified set point. Figure 1



1. Preconditioning
2. Conditioning
3. Decontamination
4. Aeration

4. H_2O_2 Decontamination Cycle Development Prerequisites

Prior to initiating cycle development, there are items that should be completed. Each of these items will affect the cycle development for the H_2O_2 cycle. As testing is completed and compiled, keep in mind that the end goal is to have an effective and efficient H_2O_2 cycle.

1. Execute FAT
    a. Factory acceptance testing should be completed prior to executing H_2O_2 cycle development. A popular approach recently is to perform as much of the installation verification (IV) and functional testing as possible during the Factory Acceptance Test (FAT) and then leverage all this testing going forward. This leveraged approach enables testing to begin early in the Commissioning/Qualification/Validation (CQV) process that can help to save time on the overall project schedule and save significant money. Testing is only executed once and is referenced or leveraged in subsequent CQV documentation. This also provides early confidence the system was fabricated and assembled in accordance with the design documentation and functions as intended. Problems that are identified during the FAT can be fixed in the vendors shop prior to shipment.
2. Perform Airflow Pattern Testing
    a. Airflow pattern testing to visualize the airflow patterns inside the isolator should be performed during the FAT and then repeated after installation once the isolator is installed on the filler. This testing can be used to select the worst case positions.
3. Perform High Efficiency Particulate Air (HEPA) Filter Certification.
    a. The upstream side of the filters is challenged with an Emory 3004 aerosol and then the filter faces are scanned with photometers to determine overall leakage.
4. Loop Checks and Calibration of Instruments for Critical Process Parameters
    a. Prior to or during the FAT instrument loop checks should be performed for all digital and analog inputs and outputs. This will provide evidence the instruments are wired correctly, the proper signals being exchanged and displayed on the HMI and the instruments are measuring within the proven acceptable range.
    b. Instruments that measure and monitor critical process parameters must be calibrated to ensure the instruments are accurate and precise within proven acceptable ranges, thereby allowing the H_2O_2 decontamination process to be properly characterized and defined.
5. Determine the Isolator Load Pattern
    a. Isolator Load Pattern should be defined with the worst case load of items inside the isolator to challenge the decontamination cycle. The items loaded into the isolator will affect the airflow, the decontamination time, and the duration of aeration.
    b. The exact quantity and location of each items needs to be defined and documented so the load pattern can be consistently repeated without variation so the decontamination cycle can be successfully re-qualified without deviations.
6. Perform Manual Cleaning
    a. The internal surfaces of the isolator including the inside and outside of each glove, the filler and ancillary equipment should be thoroughly cleaned manually with 70% IPA or an approved cleaning solution. The H_2O_2 decontamination process is a surface decontamination process and will not penetrate into cracks, crevices and other occluded surfaces if the isolator is not properly cleaned. Therefore, the H_2O_2 decontamination process is only as good as the cleaning process.
    b. This initial cleaning could be combined with a bio-burden reduction study to evaluate the bioburden post cleaning.

7. Qualify the Room Environment
    a. The background room environment must be commissioned and qualified to provide a controlled and stable environment with respect to differential pressure control, temperature and humidity, so the isolator and the decontamination cycle can be qualified.
    b. The Environmental Monitoring Performance Qualification (EMPQ) does not necessarily need to be completed prior to executing cycle development.
8. Determine the Process Sequencing
    a. Cleaning and Cooling
        i. The cool zone sterilization of the depyrogenation tunnel (if applicable), the CIP / SIP of the filling equipment and the H_2O_2 decontamination cycle should be sequenced in such a way to avoid hot surfaces during the decontamination cycle. Hot surfaces present a worst case situation to achieve the desired killing effect and should be avoided during the decontamination cycle. Optimizing the sequence of operations can reduce the overall cycle time between lots / batches.
        ii. The optimal way to sequence these activities is to initiate a cool zone sterilization of the dry heat tunnel (if applicable) and a CIP cycle concurrently. These two activities can also be sequenced in series (one after the other) if cycle time is not important.
        iii. Once the surfaces inside the isolator that were exposed to elevated temperature cool to < 40°C, the H_2O_2 the decontamination cycle can be initiated.
        iv. When the decontamination cycle progresses to the aeration phase and is approximately < 10ppm the SIP cycle can be initiated. Otherwise the SIP can be started once the aeration phase is complete and the residual H_2O_2 acceptance criteria levels have been achieved. Starting the SIP of the filling loop during aeration is a way to shave some time off of the entire cycle time if aeration is a long process.
9. Glove Integrity Testing
    a. Both physical and visual glove integrity testing should be performed prior to each H_2O_2 decontamination cycle. Physical tests usually involve one of three methods: a flow test, a pressure decay test or a trace gas sensing method to detect leaks. Each physical test method has their advantages and disadvantages; therefore, each method must be properly evaluated. Visual inspection should also be paired with physical testing to check for gross defects. Furthermore, visual inspection of isolator glove should be performed during each isolator intervention.
    b. Following the glove integrity testing, glove extenders or glove holders should be used to extend the gloves inside the isolator to eliminate folds and creases that prevent the gloves and sleeves from being fully exposed to H_2O_2. Depending on the isolator design, it may be necessary to extend the isolator glove on the outside of the isolator to execute the glove integrity testing on select gloves. In this situation a negative pressure chamber can be used to extend the gloves outside the isolator.
    c. Glove integrity testing and insertion of the glove extenders or glove holders are typically the last pre-requisite operation performed in the isolator prior to initiating the H_2O_2 decontamination cycle.
10. Determine the Biological Indicator (BI) vendor and qualify the lot of BIs.
    a. The BI vendor and the individual lots of BIs must be qualified prior to cycle development to understand the BI performance with respect to D-value. Too often cycle development is executed without knowing the D-value of the BI and how it performs within a specific isolator with a specific process.
    b. The BI also needs to be evaluated for identification and population.
    c. The gold standard BI for H_2O_2 Decontamination Cycle Development is Geobacillus stearothermophilus with a population of 1×10^6 spores per carrier on a stainless steel coupon as represented by ATCC 12980 from Apex Labs.

5. H_2O_2 CYCLE DEVELOPMENT EXECUTION

The cycle development of the H_2O_2 bio-decontamination can be executed in a progressive manner. BI qualification and Chemical and temperature mapping must occur prior to developing a worst case study.

1. BI Qualification
    a. D-value: The resistance of a BI against a defined inactivation method is expressed by decimal reduction per unit of time (min).
    d. The D-value describes the time unit it takes to reduce the test organism population 90%.
    e. Conduct a series of D-values studies to understand the response of the BI (relative resistance and behavior) and the killing effect of the corresponding cycle development parameters that created the conditions in the target isolator environment by use of a Fractional-Negative method.
    f. The D-value studies are executed by exposing pre-determined groups of BIs with multiple BIs per group to H_2O_2 vapor.
    g. At pre-defined intervals each group of BIs are removed from the isolator environment and evaluated using a growth promotion test.
    h. The goal of the fractional negative method is to achieve a total-kill of the test organism via growth tests and then determine the D-value and survival/kill window.
    i. The D-values studies are execute in a location inside the isolator that will provide the best exposure conditions to the vaporized H_2O_2. This will generally be a location immediately below the HEPA filter where the H_2O_2 vapor is being generated or being injected. There should also be no airflow obstructions above or around the BIs used in these studies.
    j. The calculation of the D-value mean is the average of three D-value evaluations plus a 25% safety factor.
    k. Use the D-value mean to design the length of the decontamination portion of the decontamination cycle.

2. Temperature, Humidity and Chemical Indicator (CI) Mapping:
    a. Thermocouples and / or temperature and humidity sensors are used to map the temperature and humidity conditions on various surfaces inside the isolator.
    b. High temperature and low humidity would be indicative of a worst case location for the killing effect of H_2O_2.
    c. These locations should be included and challenged with BIs as part of the cycle development worst case study.
    d. A chemical indicator is used to demonstrate H_2O_2 distribution within the isolator system.
    e. The chemical Indicator challenge can be executed as an independent test or executed in conjunction with temperature and humidity mapping. If the chemical indicator challenge is executed independently the CIs with the worst color change should be included and challenged with the BIs in those locations as part of the cycle development worst case study.

3. Worst Case Biological Indicator (BI) Study
    a. The worst case study is accomplished by first selecting the challenge locations inside the isolator. These challenge locations should be selected based on the results of the preceding tests that were executed as well as some geometric locations.
    b. The worst case study is executed with three (3) BIs per location. The worst case study can easily have between 100 – 150 BI Challenge locations depending on the size and complexity of the filling and isolator systems. Finally, it is critical that Engineering and C&Q are aligned with the Quality group on the identification and selection of the worst case locations. This

agreement should be formalized by having Quality review and approve the H_2O_2 Cycle Development protocol.

c. Locations to be considered / selected and included in the worst case study:
    i. The worst case airflow pattern locations can be locations were there is not turbulent flow or locations that are under equipment, devices, instruments, motors, conveyors, under windows, corners, etc. Direct observation and / or video analysis of the airflow patters will allow you to easily visualize the problem areas that may present challenges to achieve the desired decontamination effect.
    ii. The temperature and humidity mapping locations that demonstrated elevated temperatures and lower humidity should be included in the worst case study. These temperature and humidity locations may present more difficulty in achieving the desired killing effect.
    iii. The chemical indicator mapping locations that had the worst color change should be included in the worst case study.
    iv. Occluded Surfaces are all hard to reach locations where the airflow of the isolator system may have trouble delivering the vapor hydrogen peroxide to achieve the desired killing effect.
    v. Critical Zones are areas within the filling and isolator systems where there is manipulation of product contact parts including isolator gloves and sleeves. Additional locations should be selected to properly challenge the isolator system to consistently and effectively achieve the desired decontamination effect.
    vi. The E-Beam tunnel (if present) is typically part of the surface area that is decontaminated with the isolator system. The E-Beam should be included in all of the appropriate testing to evaluate the system during H_2O_2 cycle development.
    vii. Entrances and Exits to the isolator system need to be included in the worst case location study to properly evaluate the isolator system. This should include all transfer locations such as Rapid Transfer Ports (RTPs), transfer isolator locations and piping connections.
    viii. BIs should also be placed on gloves and sleeves. Typically, BIs are placed in two general positions: The first on the sleeve in the most challenging position as the gloves are extended into the isolator and secondly on the fingers of the gloves. To determine the final sleeve position(s), each glove extender length needs to be determined, fixed and consistently replicated for each decontamination cycle.
    ix. Consult the quality group to see if there are locations inside the isolator they want to see challenged as part of the worst case BI study. This strategy may eliminate second guessing and questions as the CQV activities proceed and the protocols and summary reports are approved.

4. Aeration Study:
   The aeration study is executed by running the final cycle that was determined through the cycle development studies. This final cycle is then initiated.
    a. When the cycle transitions to the aeration phase use a Draeger hand pump and Draeger tubes to evaluate the residual H_2O_2 levels at various time points.
    b. When two consecutive residual H_2O_2 readings are in the same Draeger Tube range the aeration endpoint is established. However, the endpoint can only be established if the minimum required H_2O_2 level has been achieved in accordance with the residual ppm level defined in the User Requirements Specification (URS).
    c. Note: The URS endpoint is either established as an Operator Exposure Level (OEL) requirement of ≤ 1ppm or a product specific requirement to prevent oxidation and degradation of the drug product being filled within the isolator environment.

5. PERFORMANCE QUALIFICATION:

The PQ for the H_2O_2 decontamination cycle shall be performed by running three consecutive decontamination cycles with three BIs per location. The PQ runs will use the parameters and conditions that were established during the cycle development work. If the filling system requires CIP and SIP these activities should be included in the PQ test plan and protocols.

An alternative approach is to use a reduced decontamination phase of the decontamination cycle to execute the PQ for a more challenging qualification.

1. The number of BIs locations used in the PQ can be reduced vs. the total number exposed during the worst case study.
2. The reduced number of BIs can be based off the findings and results for each of the individual tests during cycle development.

For example, the number of BIs for the PQ Study can be determined from the worst case locations identified during Temperature and Humidity Mapping, chemical indicator study and from the airflow pattern testing. Once this strategy is defined and the number of BIs is determined this should be applied to the periodic requalification procedure.

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AGENDA

8:30 - 9:00 **Registration Open & Continental Breakfast**

9:00 - 9:15 Opening Remarks - Michele Creech, Quality Operations Manager, Grifols

9:15 - 10:15 Session 1

GLP vs GMP
Dominique Pifat, Ph.D., *Sr. Director Marketing and Training Intercontinental*, Grifols
This presentation addresses the practical differences and similarities between the GLP and the GMP regulations. Most important to note is that both sets of regulations have the force of law and one is not more stringent than the other. Special emphasis will be given to overall roles and responsibilities, quality assurance, equipment requirements and documentation. Although there are clear differences in terms of where the regulations apply and how they are implemented, the spirit of the regulations is very similar.
Dominique Pifat, PhD, is currently the Senior Director of Marketing and Training for International at Grifols (formerly Talecris Biotherapeutics). Prior to that she was Senior Director of Pathogen Safety for Talecris biopharmaceuticals where she was involved in the viral and prion safety of biological products. Dr. Pifat began her carrier establishing and characterizing animal models for the development of viral vaccines and antiviral drugs and spent most of her carrier in the development of biological products. Dr. Pifat established GLP-compliant laboratories for the US

Army, Bayer Biologicals and Talecris Biotherapeutics. Dr. Pifat received a bachelor's degree in Biology and in French Literature from Goucher College in 1979 and a PhD in Microbiology and Immunology from the University of Maryland Medical School in 1985. Dr. Pifat also completed a Global Executive MBA at University of North Carolina, Chapel Hill in May 2008.

10:15 - 10:45 Break + BTEC Tour

10:45 - 11:45 Session 2A & 2B - Concurrent Sessions

SESSION 2A

Validating your Rapid Micro Method

Dr. David Jones, *Director of Technical Services* , Rapid Micro Biosystems

The question often asked by companies evaluating rapid micro methods is "what does it take to validate?" Much like the different types of RMM approaches, the validation process can vary. Validation of the RMM solution requires understanding both internal and external requirements to appropriately validate the RMM solution. During this session learn the different requirements for validation and review sample validations that have been performed.

David has more than 20 years experience in analytical method development, validation and equipment optimization in the diagnostics industry, with a number of start up companies including Unipath. David then spent six years at Chemunex where he introduced rapid microbiology methods to the market as Director of QA and Regulatory Affairs. More recently David was at Wyeth Biopharma leading the evaluation and validation of rapid micro methods and new technologies to improve laboratory efficiencies. David has a BSc in Biochemistry and a PhD from London University in steroid endocrinology.

SESSION 2B

FT-NIR Spectrophotometry - Validation Hurdles, Chemical Issues and Benefits

Jerry Dalfors, *Principal*, JD Technologies and Life Coaching

Near-infrared (NIR) spectroscopy has become an essential method of Process Analytical Technology (PAT) in the pharmaceutical industry. This reflects the emerging trend for more and more analytical tests that could previously only be done in the laboratory to now be used in production. This leads to challenges in Confidence, Robustness, Repeatability, and Accuracy, since known (and sometimes unknown) variables that can cause false positives, false negatives or minor data variation might not be readily detected as biased data. Thus robust validation is required. The ultimate objective of this work is to gain critical knowledge of a pharmaceutical manufacturing process.

Mr. Dalfors has had extensive (39 years) consultative, technical and managerial experience in the development and manufacture of highly regulated biopharmaceutical products including injectables, biologics, medical devices and oral dosages as result of having been a "rocket scientist", MBA business training, graduate level statistics and Electrical Engineering Technology. He has a BS in Microbiology. Prior to his current position as Principal, JD Technologies, he held management positions with major pharmaceutical and biotechnology companies as Acting VP of Operations, Div. Dir. Pharmaceutical Operations; Dir. Technical Services; Validation Manager; Marketing Manager; Project, Process and Instrumentation Manager/Engineer, and Quality Assurance Testing Manager. Since starting JD Technologies, he has assisted more than two dozen clients with their Process Monitoring and Automation, Documentation Systems, CAPA Management, FDA Briefing Documents, Validation Efforts, Facility and Product Design, mock FDA audits for Regulatory Compliance Issues, and has written many submission documents for product and facility approval/licensing. He was recently one of the speakers at the World Vaccine Congress April 11-14 of this year.

11:45 - 1:00 **Lunch + BTEC Tours**

1:00 - 2:00 Session 3

Lean Six Sigma Case Study

John Wass, *Validation Scientist*, Commissioning Agents, Inc.

A lean six sigma case study will use various tools such as CTQ trees, value stream mapping, kano diagrams, and cause-and-effect diagrams to evaluate a hypothetical process to receive, test and release a sample. Challenges in Lab Design, Instrumentation, Methods, Personnel, and Sample Management will be discussed.

John Wass is a Validation Scientist and degreed chemist with six years experience in the fields of analytical chemistry, polymer synthesis, lab start-up, LIMS configuration, and process control system migration. He earned his B.Sc. in Chemistry with a specialization in ACS certified Biochemistry at the University of Virginia, where he spent a year researching solid phase extraction techniques for application in a fully integrated microdevice capable of genetic DNA analysis. John spent the subsequent three years at a medical device start-up in RTP participating in the development and characterization of synthetic, resorbable surgical sealants from concept through to commercialization. He leveraged this experience at a greenfield biotech facility where he assisted for over a year with the start-up of the QC analytical and raw materials lab, focusing on instrument qualifications, method transfers and a global LIMS implementation. John garnered an intimate knowledge of the QC business process while configuring the LIMS system, where facility, instrument and method design were critical to a successful implementation that could augment the existing QC process. He is currently applying this knowledge to a DeltaV process control system implementation at another cGMP facility.

2:00 - 3:00 Session 4

Using MALDI-TOF for Microbial Identifications

Gary Kruppa, Ph.D. , *Vice President Business Development*, Bruker Daltonics, Inc.

The MALDI Biotyper employs MALDI-TOF technology to produce a protein fingerprint which can be used with a database of such fingerprints to identify microbial species within minutes after positive culture, with a consumables cost per test of about $0.20, and covering a wide range of Gram positive and Gram negative bacteria, yeast and fungi. The principles of MALDI-TOF will be discussed as they apply to obtaining protein fingerprints of microorganisms. The workflow for sample preparation and microbial identification using the MALDI Biotyper will be presented, and applications to clinical, industrial, and pharmaceutical microbiology will be discussed.

Gary Kruppa received his B.S. in chemistry from the Unversity of Delaware in 1982, and his Ph.D. in chemical physics from the California Institute of Technology in 1988. Until 2001 he worked at Bruker Daltonics, in the area of Fourier Transform Mass Spectrometry (FTMS). He then joined Sandia National Laboratories to pursue research in the applications of FTMS to the study of bio-molecules. In 2004 he re-joined Bruker Daltonics and is Vice President for Business Development. His interest in mass spectrometry applied to the study of bio-molecules led to his involvement with mass spectrometry based products for research in clinical proteomics and in clinical, environmental and pharmaceutical microbiology. Dr. Kruppa has more than 30 years of experience in mass spectrometry applied to chemical and biological applications, and has co-authored more than 40 peer reviewed publications and two book chapters.

3:00 - 3:30 **Break + BTEC Tour**

3:30 - 4:30 Session 5

Regulatory Discussion Topics for Handling Samples and Testing from R&D through Phase III Clinical Trials
Patti Rossman, *President*, Globiox and Ron Hinkel, *Director of Quality*, BioReliance
Regulatory Requirements (GMP, GLP, or GCP/CLIA) should be followed with each type of sample and each kind of test during pharmaceutical/biologics product development from R&D through Phase III clinicals. Examples of biological and chemistry assays will be reviewed to explain how this data is used, which Regulations apply, during the different phases of the drug development life cycle. Participants will be given a tool to aid in determining the appropriate Regulations to follow.
Ron Hinkel and Patricia Rossman developed their vision of appropriate Regulatory requirements for testing associated with the development of pharmaceutical and biologics products based upon their combined experience providing testing and consulting services to 600+ clients and regulatory guidance published by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH). *Mr. Hinkel, Director of Quality at BioReliance, has many years of experience in the Contract Research Organization industry, having held prior Quality and IT/Validation positions at Centocor (Johnson and Johnson) and WuXi AppTech. Mr. Hinkel also served on the FDA – PDA task force for Part 11. Currently he provides leadership for BioReliance's US Biosafty testing divison. Mr. Hinkel is a graduate of Lehigh University holding a BS in industrial engineering.* *Ms Rossman, President of Globiox, began her career as a medical technologist and has many years of experience in laboratories and consulting to laboratories. She has held Quality and Validation positions at Abbott, American Red Cross, Esoterix, LabCorp, and Pharmaceutical Services Corporation. Currently she provides leadership at Globiox, which provides Quality and Compliance services to the Life Science industry. Ms Rossman is a graduate of the University of Texas at Austin, and the Software Quality Institute in the Department of Engineering, University of Texas at Austin. She is a Certified Software Quality Engineer (ASQ).*

4:30 Closing Remarks

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Implementing Single-Use System in Existing Facilities

By Kim L. Nelson, PhD, CRB Consulting Engineers

Switching from traditional equipment to disposables can deliver savings while maintaining sterility, but successful retooling demands first considering numerous process and logistical issues.

Biopharmaceutical processes and manufacturing facilities can change many times over their operational life, as plants are adapted to accommodate new products and processes are modified to ensure commercial success.

In some manufacturing settings, disposable process equipment can offer significant advantages, improving flexibility, speeding installation and startup and reducing water consumption.

Today, the majority of biopharma manufacturing plants still use stainless steel process equipment, storage tanks and transfer lines for most of their process needs. However, this is changing as a growing number of manufacturers adopt disposable single-use systems and flexible tubing.

Oft en, disposables are discussed as if they could simply be dropped into any given biopharmaceutical manufacturing operation. In reality, one cannot just replace a traditional steel tank and connector system with a disposable system without making other modifications and considering many issues. Each type of system imposes its own limitations and requirements on a facility. Changes in traffic flows, airlock design and materials and waste flow must also be closely considered.

Some situations where single-use systems may have particularly relevant applications include:

- Facilities undergoing renovations and revamps to accommodate a new product. An example would be a product with a different purification process that requires different volumes of buffers.
- Small-volume applications involving 2000L or less.
- Processes that are new and thus aren't well characterized.

This paper will focus on implementing disposable process equipment in existing facilities that also utilize stainless equipment, highlighting the logistics and design issues that must be addressed to ensure success during both the initial installation and ongoing operations.

SPEEDING TIME TO MARKET

Time to market represents perhaps the single largest driver in adopting disposables for clinical manufacturing and early commercial manufacturing. Both traditional and disposable process equipment have their own advantages and disadvantages, as summarized below, but adopting single-use systems where appropriate allows quicker installation and decreased validation — both of which translate into getting product out the door faster.

Disposables impose different validation requirements than traditional equipment. Where stainless steel tanks and transfer lines must be clean-in-place (CIP) and steam-in-place (SIP) validated, disposables must be tested for product compatibility and the presence of extractables and leachables. Such testing can be done in advance of a facility's completion (in parallel with construction). Once the compatibility, leachable and extractable testing is done, one may select a larger or smaller bag as a process requires.

With stainless systems, the extensive cleaning and sterilization qualification and validation cannot begin until the mechanical completion of construction. In contrast, disposable equipment allows manufacturers to qualify use of the plastics and equipment early in the plant design and construction phase, so they can "hit the ground running," shaving startup times.

Traditional Stainless Steel Process Equipment	
Disadvantages	**Advantages**
Large voles of water needed for CIP	No limits on tank size
High capital and operating costs	Higher level of automation feasible
Unavailability, due to CIP and SIP	Potentially lower labor costs
Lengthy construction and validation time	Containment is possible
Inflexible with regard to process changes	No solid water disposal issues
Requires a large footprint (in some cases)	
Disposable Process Equipment	
Disadvantages	**Advantages**
Higher costs for consultants	Quicker installation relative to stainless steel
Achievable flow rates are limited by connectors	Reduced process utilities demands, particularly for WFI and clean steam
Higher warehouse concerns	Numerous suppliers
More complex layout considerations	Potential savings in cleanroom footprint
Solid waste disposal issues	Reduced validation time and cost
A more manual operation	Significant labor savings for CIP and SIP
May not be appropriate for hazardous materials	

Table 1. Relative merits of stainless steel vs. single systems

Functional Area	Traditional	Single Use	Comments
Inoculum prep	Spinners	Wave bioreactor Shake flasks	Very suitable
Seed bioreactor	SS bioreactors	Wave bioreactor Hyclone SUB	Very suitable
Production bioreactors	SS bioreactor	Hyclone SUB Xcellerex Wave	Up to ~1-2000L Up to ~1-2000L Up to 500L
Solution prep	SS mix vessel	Hynetics Hyclone ATMI	Up to 10,000L Up to 2000L Up to 1000L
Storage bags	SS mix vessel	Stedim Hyclone Millipore	Up to 2500L Up to 2500L Up to 2000L

Table 2. Some examples of scale limitations in single-use applications

Disposables can also decrease the time required for equipment turnaround. With disposables, replacing a bag requires about 30 minutes, half of that time for removal of the bag and disposal, and the rest for inserting a new bag and connecting it. CIP, in contrast, typically requires one to four hours (or longer), depending on the complexity of operations involved. Similarly, for product changeover in multi-product facilities, the ability to merely remove a bag and tubing system is a tremendous advantage, rather than

CIP, swab testing and SIP, and in the worst case, a revalidation of the equipment for the new solutions or product. In the product changeover, if different number or volumes of solutions are required, bags allow one to simply use larger bag holders, or more of them.

IMPLEMENTING DISPOSABLES

Once the decision is made to consider disposables, one must examine the key issues of implementing them in any existing manufacturing facility. The obvious applications include solution holding situations. Other opportunities include, but are certainly not limited to:

- Buffer and media hold containers
- Solution mixing/prep operations
- Bioreactors
- Vent filters, sterilization and clarification filters
- Tangential-flow filtration operations (small-scale only at present)
- Harvest or intermediate product containers
- Transfer hoses
- Final product containers or
- freezing containers
- Filling heads in a fill line
- Connectors
- Valves (tubing pinch valves)
- Centrifugation

Generally, implementation can take place in two or more incremental stages. Initially, one examines a manufacturing schematic and considers potential use points for single-use systems, identifying areas or unit operations where single-use systems may be inserted without overt problems. One then identifies secondary applications that may require experimental confirmation of their appropriateness, such as product contact, separation systems or bioreactors.

In any implementation of disposable process equipment, a myriad of different issues must be considered:

- **The specific application**
  - The process must be mapped.
  - The given system's suitability for the process scale must be determined.
  - Risks must be fully assessed.
- **Materials of construction within the disposable process equipment**
  - Evaluate their compatibility with product and process. Note that vendor data typically reflects results of tests run with the most widely used commercial buffers. Manufacturers must confirm testing for special buffers and solvents, and must qualify and validate stability and shelf life.
  - Test for extractables and leachables.
- **Disposables functionality**
  - Connections
  - Interfacing between rooms
  - Sampling
  - Mixing and temperature control requirements
- **Ergonomics**

    - Bag weights and movement
- **Logistics**
    - Warehouse inventory levels
    - Supplier qualification/redundancy
    - Bag waste removal and disposal
- **Facility design**
    - Bag weights and floor loading
    - Movement through corridors (including pallet jacks)
    - Simulations of bag usage, queuing and movements
    - Staging space for containers
    - Layout adjacencies
    - Robust flooring and wall materials
    - Material, equipment and waste flows
    - Corridor and airlock requirements
    - In-process storage needs
    - Warehouse space requirements
    - Utility requirements and consumption

PROCESS SCALE

It is essential that the disposable equipment selected be adequate for the scale of the process. Table 2 summarizes some selection guidelines. Generally, decisions will be made based on:

- Commercial availability
- Risk/reliability of supplier
- Ergonomics and ease of operation
- Liquid transfers
- Aseptic connections
- Cost

In situations where the process or batch size is too large, consider using bags where you can — smaller buffers, bioreactor feeds, etc. For buffers, one could consider in-line dilution using buffer concentrates for large requirements. If the quantities are on the only slightly over, consider ganging bags together for larger volumes (e.g. 2x2000L), or investigate bigger bags (bags of up to 10,000L are being used for media compounding, and custom bags are being routinely supplied in volumes of 4000+L). Depending on the situation, it may be a better solution to stay with stainless steel if production throughput demands require 15,000L+ bioreactors.

In all cases, it is wise to do an economic analysis to make sure it makes sense in light of the cost-of-goods goals.

LAYOUT ISSUES

Layout requirements will also change with disposables. In deciding whether disposable process equipment will be a viable choice for a given process environment, it is critical to look at the level of activity and the size of the operation. For example, the material flows with disposables often involve the circulation of large numbers of totes and drums, which must be wheeled up and down corridors. More staging areas will be needed for filling operations, as well as emptying and storage. Maintaining adequate staging space to avoid cluttering corridors is important; this in turn requires an understanding of inventory levels and material movements.

Generally, the use of disposables will require larger airlocks, particularly if there are any shared material and personnel entry or exit points. To maximize safety, materials and personnel airlocks are best separated, and the materials airlock should be large enough to allow the totes or drums that are entering or leaving to be staged off to one side so that the emergency egress path is not blocked.

Waste flows are also important in a facility utilizing disposables heavily. Flows of used bags heading to the trash will be heavier, and warrant optimization of exit paths and location of elevators to minimize this movement. The goal is to move waste out in the most effective manner, while minimizing crossing with product or materials coming in.

In multi-floor facilities, two approaches may be taken. One is to locate the solution preparation and filtration systems, together with the users, on the same floors. Alternatively, one can locate the preparation operations on the floor above, and use gravity to assist in delivery of the buffer or media. Transfer of totes or drums between floors by elevator is awkward and usually requires the use of airlock vestibules in front of the elevators.

Staging spaces will be critical in order to keep corridor areas uncluttered. Often, facilities designers and engineers fail to consider these issues when implementing disposables, or the owners needs expand in the future beyond available staging space.

Don't neglect floor and wall material requirements. There'll be a lot more traffic and movement of larger containers with disposables than there typically is with fixed equipment, so materials of construction must be robust.

With disposable process equipment, storage is a key consideration. Disposables can help save storage space in some installations. Disposable bag systems typically require less floor space within process rooms than stainless steel vessels, but they also pose plant layout challenges. Different implementation strategies can be applied, including bag-in-place, moveable totes and use of tubing pass-thrus.

Hallways must allow for easy movement of pallet tanks. Can this be achieved in the existing facility design? With pallet movements, two issues must be addressed – 1) safe passage of staff around the pallet tank while it is being moved, and 2) maneuvering the pallet around corners and through doorways.

Other important considerations are the room height available for tote storage, and airlock and hallway sizes. These may be too small in existing facilities to accommodate disposables.

TRANSFERS AND CONNECTIONS

Another critical issue is material transfers between rooms. Sartorius Stedim's RAFT system is one option available today to facilitate transfer. The RAFT system provides an absolute seal between rooms. An alternative is to use an Iris valve pass-thru. Iris valves are used in powder handling applications, and, when applied here, allow tubing sets to be squeezed into the center area as the valve is tightened. This system is convenient for passing tubing between rooms and allows for multiple tubing sets to be passed through simultaneously, but it also has a convoluted surface and will prove more difficult to wipe down.

Within rooms, routing and organizing tubing is important if one is to avoid draping tubing haphazardly or having tubing lying on the floor. Both tray and hangar installations are available for routing the

disposable tubing. Trays are perhaps more difficult to wipe down, but have a larger capacity. Tubing "J" hangers are easier to wipe down, but cannot carry as many tubing sets.

TO CHANGE OR NOT TO CHANGE

Depending on the process and product involved, you may opt to change to disposables in whole or part, or to remain with stainless steel equipment. The first step in making the decision is asking the following questions:

- Will the existing process be modified?
  - Will it entail a completely different process?
  - Will more buffers or different buffer volumes be required?
- Are there shortages of water available for CIP?
- Is the production schedule limited by turnaround time?

Simulation can be extremely helpful in making a decision whether or not to implement disposables, and in estimating the potential impact of disposables use on existing facilities and operations. One useful simulation outcome is the assessment of bag inventory levels based on usages and weeks of supply on hand. Another tool of simulation is the industrial engineering study of time, motion and queuing.

Simulation can also be used to determine the potential impact of warehouse inventory levels, buffer storage room(s) and staging spaces, movement of drums and totes, and buffer batch sizes.

Economics will also guide the decision. While the use of disposables may not be compelling for a mature product, it can greatly increase speed to market for a new one.

Economic analysis can be very sensitive to throughput and bag usage. Remember that not all disposable systems are "single-use." With some disposable bioreactors, use of perfusion media bags means that bags are not changed until the end of the production run, when the disposable bioreactor is replaced. In addition, operating a line at reduced capacity can push the break-even time for investment in stainless steel equipment well beyond the 2.5-year point.

Ultimately, demand for the given product, schedule and cost will dictate the choice between stainless steel and disposable process equipment. In some cases, staying with stainless steel production systems may be the best option. However, an economic analysis and time-motion simulations are recommended to complement the schedule and technical drivers so that you can make the best choice for your manufacturing requirements.

Disposables and single-use systems are particularly useful in situations where volumes are moderate, and turnaround or product changeovers are frequent. These situations are characteristic of clinical-trial material manufacturing, early launch, and perhaps full manufacturing for some products.

OVERCOMING OBSTACLES

What can be done when there are technical challenges — for example, when a process or batch size is too large? Some rules of thumb:

- Use bags wherever possible — for smaller buffers, bioreactor feeds, and the like
- Consider in-line dilution using buffer concentrates for large requirements
- Consider ganging bags together for larger volumes

- Investigate the use of larger bags (for example, bags capable of holding up to 10,000L are being currently being used for media compounding)

Options are also available where cold processing is required. Generally, cold rooms work well for keeping cold liquids cold, but if rapid cooling or heating is needed, jacketed or non-jacketed totes in cold rooms will not suffice. Consider that a 1,000-L pallet tank bag placed in a cold room may take more than a day to cool down sufficiently. Using in-line heat exchangers to cool or heat solutions as they are transferred into or out of the bags increases efficiency.

Suggested Reading

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