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Safety Evaluation of a Flexible Engineering Control System

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This article presents a study performed to evaluate the fitting, removal, and disposal of contaminated filter cartridges using a flexible containment system.

Introduction

A wide variety of industries face significant occupational hygiene and chemical containment challenges due to the increased manufacture of more potent drugs and chemicals. The manufacture and use of potent substances with Occupational Exposure Limit values (OELv) <1µg/m^3 often requires the development and use of containment systems. This may include designs for new manufacturing facilities and the retrofitting of older facilities.

When selecting engineering controls for the management of particulate emissions, the choice of options is vast and selection is usually dictated by performance, suitability, and cost.[1] Total enclosures are commonly used for control of particulates in the chemical and radiation industries,[1,2] where designs vary from rigid glove boxes to flexible glove bags. Many of the fixed containment options are expensive; therefore, they are outside the budgets of Small to Medium size Enterprises (SMEs). Due to financial constraints, many SMEs resort to the use of elaborate (and often costly) Personal Protective Equipment (PPE) as their ultimate control measure. Both the use of fixed containment options and PPE can pose challenges to the end user.

A task which often requires the use of exposure control and that is commonly conducted in the chemical and pharmaceutical industries is the filtration of either a liquid or particulate chemical agent. The filtration process for pharmaceutical products is conducted by a variety of techniques; one of the most common types of filters used (for polishing wet products and for trapping dry particulates) is the cartridge filter.

In the majority of filtration operations, the filtration itself, whether wet or dry, is normally

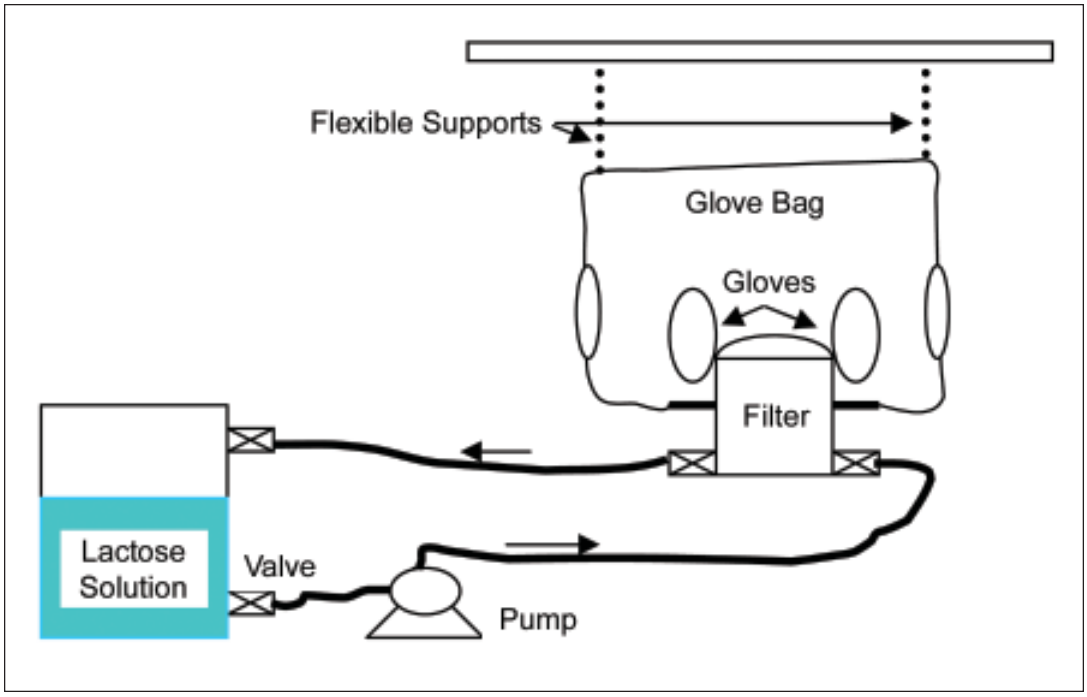

Figure 1. Outline of liquid filtration test rig.

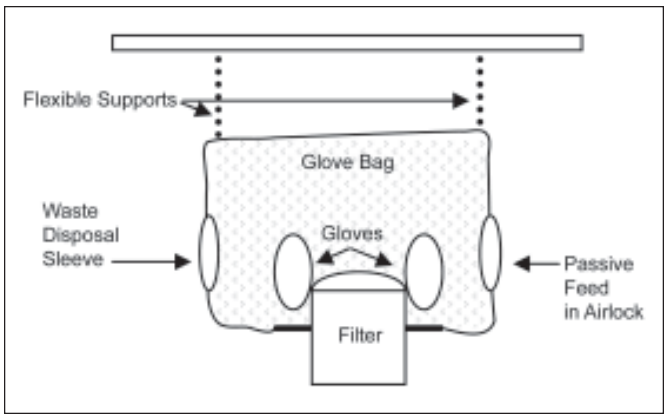

Figure 2. Outline of dry filtration test rig.

conducted under contained conditions; where the cartridges are contained within a secure housing and pose no containment problem while in situ. However, a potential exposure issue may arise when used cartridges are being removed. Traditional containment systems used in this situation include rigid glove boxes, 'dry break coupling,' and/or the use of PPE. The former system always requires considerable capital investment and the latter releases the product into the facility, necessitating further cleaning which again requires the use of PPE.

There is often no or limited occupational hygiene exposure data estimates available for current containment systems. And most of the designs available are for routine manufacturing tasks and not for non-routine activities where the potential occupational exposure risk is often the greatest, e.g., maintenance or emergency activities. The task analyzed in this study includes the fitting, removal, and disposal of contaminated filter cartridges using a flexible containment system. Inadequate containment during this unit operation could result in over-exposures to hazardous substances, expensive decontamination, clean up requirements, and significant product quality concerns.

The Use of Flexible Containment in Industry

A viable alternative to rigid containment systems is the use of flexible containment, e.g., 'glove bags.' Flexible systems aim to provide containment in situ when potential high risk exposure unit operations are being performed. The advantage of using flexible containment systems is that they can be adapted easily to any facility, without modifying equipment and incurring significant capital cost. The flexible containment design also is more ergonomically friendly and is an especially useful containment solution for retro-fitting older facilities. Flexible containment designs also can be continuously used subject to the replacement of attachments such as sleeves.

The following include a number of areas where flexible containment systems are being used successfully:

- filter changing (all types)
- dry powder and liquid sampling
- powder dispensing
- sample handling in laboratories
- removal of equipment from process lines
- dryer vent sock changing
- centrifuge cloth removals
- barriers for inspection of vessels and lines
- seeding process vessels
- powder and liquid charging etc.
- asbestos removal[3]

These flexible systems are not only a containment solution for the pharmaceutical industry, but are applicable for any industry that requires the containment of products. Flexible containment systems have proved especially valuable in GMP manufacturing environments where there is a risk of two-way contamination.[4]

As pharmaceutical compounds become more potent and pose a greater challenge from a containment perspective, greater efforts are required to assess the performance of a containment device before introduction to the workplace.[3] Some have assessed the containment capability of a glove bag in the context of asbestos removal. However, while data from other industries suggest that the containment capability data for flexible systems are directly comparable to rigid systems, these data are company-specific; therefore; they are not widely available. However, there is data to support some exceptions.[5] It is likely that flexible containment provides other operational advantages apart from containment, e.g., time and labor savings, over rigid systems, but these have not been formally assessed. To redress this, the objective of the present study was to carry out an assessment of both the ergonomic and containment capability aspects of two glove bag designs to be used as the primary containment device for the unit operation of changing product-contaminated wet and dry cartridge filters.

Methodology

Materials

The glove bag designs tested in the study were manufactured from anti-static polyurethane and were attached to the filter housing by means of a clamping arrangement. The first glove bag design was a closed system, the second design had a built in passive 'feed in' airlock and a detachable 'waste disposal' sleeve. Two experimental test rigs were built; one to carry out the safety review of the closed glove bag system on a liquid filtration system, an outline of this test rig is shown in *Figure 1*. The second experimental test rig to complete the safety review on the glove bag with the passive 'feed in' airlock and detachable 'waste disposal' sleeve on a dry powder filtration system, an outline of this test rig is shown in *Figure 2*. In these trials, the glove bags were maintained at normal atmospheric pressure and air was exhausted through a HEPA filter welded to the glove bag.

Using the equipment set up as detailed in Figures 1 and 2, a containment capability survey and ergonomic assessment was complete. A surrogate material, micronized lactose, was selected for the containment capability study, the primary aim of which was to estimate the potential personal exposure level when using the flexible unit to introduce and install new

filters and remove and dispose used contaminated filters. The containment capability study was conducted following documented guidelines.[6]

Experimental Set Up

Liquid Filtration Test Rig

5kgs of Lactose was dissolved in 40 liters (8.8 gal) of water at room temperature and re-circulated through a multi stack fluid purification unit. The unit used contained five 10 inch (254 mm) (length) cartridge filters. The closed system glove bag was attached to the filter housing unit. The glove bag was initially primed with 30 new filters to allow for completion of the assessment without requiring further access into the system. The unit operation using the glove bag under investigation had the following distinctive steps:

1. insertion of five new cartridge filters into housing unit
2. circulation of lactose solution though the filter housing unit
3. removal of contaminated filters from filter housing
4. deposition of contaminated filters into 'waste disposal' sleeve
5. fitting of new filters into the filter housing unit

The unit operation was repeated six times. To further challenge the containment capability of the glove bag design after the first trial, the previously contaminated filters were re-used as the new filters for introduction and fitting into the filter housing for successive trials.

Dry Powder Test Rig

The second glove bag design with the built in passive 'feed in' airlock and detachable 'waste disposal' sleeve was used in this set up. A new cartridge filter was inserted into a single 10 inch (254mm) filter housing. The unit operation using the glove bag under investigation had the following distinctive steps:

1. insertion of one new cartridge filter into housing unit through passive airlock
2. distribution of 250g (0.55lbs) of lactose inside the filter housing and working chamber of the glove bag itself
3. removal of contaminated filters from filter housing
4. deposition of contaminated filters into 'waste disposal' sleeve
5. removal of section of 'waste disposal' sleeve containing contaminated filter cartridge
6. fitting of new filter into the filter housing unit

The unit operation was repeated six times. However, the step of removing the contaminated filters from filter housing and their disposal into the 'waste disposal' sleeve was only completed during trials three, four and six. To further challenge the containment capability of the glove bag design, the same glove bag was used for successive trials without cleaning between trials.

Collection of Exposure Data on the Unit Operation Without the Use of the Glove Bag

As no work place data was available on the potential workplace exposure concentrations expected when removing contaminated filters from filter housings, the unit operation filter removal without the flexible glove in place also was studied here using the placebo material. This test was carried out after the test trials were completed, using both the single and the five filter cartridge units without the use of the glove bags.

Lactose Air Concentration Sampling

Personal breathing zone samples were collected from the operator who performed the unit operations. Fixed area sample locations around the filter housing unit, the operator side of the glove bag, were selected after visualization of the airflow in the test room using an air current tester prior to the study. Four area samples were taken at locations 90°, 180°, 270°, and 360° from the filter housing unit at distances of between 2.1 and 2.6 meters (6.8 to 8.53 ft) from the equipment set up. All area and personal samples were collected using glass fiber filters and IOM sample collectors. Samples were collected at an average flow rate of 2 liters/min (0.44 gal/min) and calibrated for flow rate before and after sampling using

Sample Location /Sample Type	Number of Samples	Average Result ($\mu g/m^3$)
Area Samples*		
Background 90°, 180°, 270°, and 360° to the filter housing pre trial	4	$< 0.04\ \mu g$
90°, 180°, 270°, and 360° to the filter housing during trial 1- 6	24	$< 0.04 - 0.78\ \mu g/m^3$ average = $0.042\ \mu g/m^3$
Background 90°, 180°, 270°, and 360° to the filter housing between trial, 1&2, 2&3, 3&4, 4&5, 5&6	20	$< 0.04 - 0.85$ average = $0.14\ \mu g/m^3$
Background 90°, 180°, 270°, and 360° to the filter housing Post final trial 6	4	$< 0.04\ \mu g$
Personal Samples		
Trial 1 - 6	6	$< 0.04\ \mu g$
Limit of Detection = $< 0.04\ \mu g$/filter		
*All area samples were taken operator side of the glove bag.		

Table A. Summary of area and personal sample air concentration data ($\mu g/m^3$) for the five cartridge filter housing.

a primary flow meter. Personal samples were taken in the breathing zones of the operator performing the unit operation. Area samples were sampled at breathing zone height to better understand the potential for release of material from these operations into the surrounding test laboratory area. Personal and area samples were run for the duration of the unit operation 10 to 15 minutes and for a minimum of 20 minutes after the unit operation was complete. The unit operation was repeated six times (trial one to six). Background samples were run prior to trial one, between each trial and after the final trial (trial six). Temperature and humidity was measured throughout the study and found to vary from 22.8 to 24.2°C and 49-52% respectively. The air change rate in the test laboratory was measured as 5.1/hour.

Analytical Sample Analysis

Samples were analyzed for lactose by the Institute of Occupational Medicine, Edinburgh, using a validated lactose air monitoring method. One quality control spike (0.68 mg/filter) and one blank sample per 10 actual samples were included in the study. The average recovery of the spikes was 104.7%, within the acceptable range for the analytical method. The limit of detection of the lactose air monitoring method was 0.04 mg/filter.

Real Time Particulate Sampling

Airborne particle counts were obtained using a laser-based particle counter, which sampled a 2.8 x 10^{-2} m^3 volume of air in one minute, and sensed particles with cut-off diameters of 0.3 µm, 0.5 µm, 0.7 µm, 1.0 µm, and 5µm. The particle counter was positioned to monitor around the filter housing at a distance of approximately 1 meter from the filter unit. A baseline measurement of particle counts per minute was obtained during a period of approximately 10 minutes prior to each filter-changing trial, followed by a particle count during each filter-changing trial. Additionally, a count was obtained after the complete survey, comprising six trials, was complete.

Ergonomic Assessment of Operations

In order to assess the ergonomics of the operations involved, the operation was divided into four main tasks:

1. removal of lid from filter housing
2. removal of filters from housing and placement into the waste filter glove sleeve (five filters per change out)
3. filter replacement – from clean glove sleeve into filter housing
4. replacement of filter housing lid

Completion of the task was averaged to be six minutes for all four steps of the operation. This time requirement may vary in industrial practice because it depends on operator experience. Each step of the operation was viewed six times for the assessment to ensure accurate results.

The ergonomic assessment was completed on operations using the five cartridge filter housing unit; an alternative to this filter system is the single cartridge filter housing system. The operations using the single cartridge filter housing unit were not observed; however, some of the findings of this study can be extended to the use of the single cartridge filter housing unit (due to similarities in dimensions, weights, etc. between the two filter systems).

Assessment Techniques Employed

Qualitative Manual Handling Risk Assessment

A qualitative manual handling checklist was used to assess the lifting tasks involved in the operation.

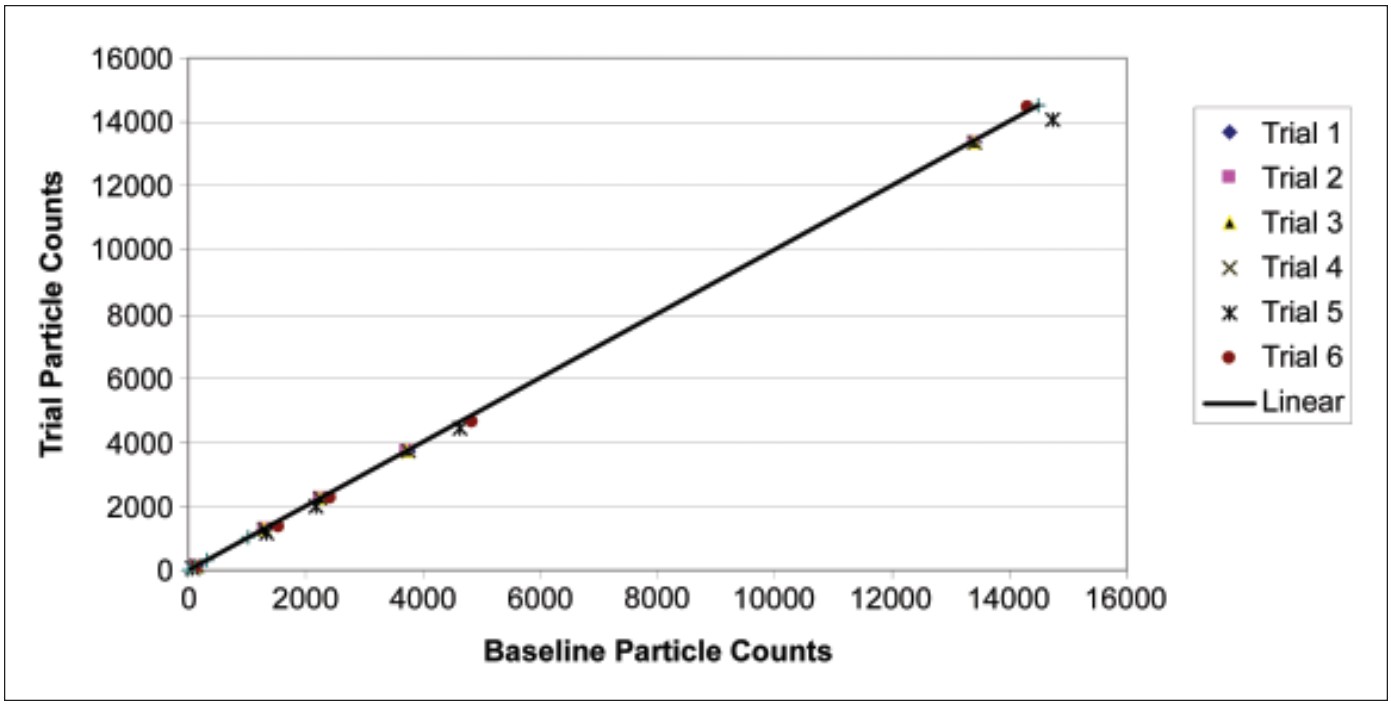

Figure 3. Particle counts vs. baseline counts during dry powder trials.

Location Title	Number of Samples	Average Result ($\mu g/m^3$)
Area Samples*		
Background 90°, 180°, 270° and 360° to the filter housing pre trial	4	< 0.04 μg
90°, 180°, 270°, and 360° to the filter housing during trial 1- 6	24	< 0.04 μg
Background 90°, 180°, 270°, and 360° to the filter housing between trial, 1&2, 2&3, 3&4, 4&5, 5&6	20	< 0.04 μg
Background 90°, 180°, 270°, and 360° to the filter housing Post final trial 6	4	< 0.04 μg
Personal Samples		
Trial 1 - 6	6	< 0.04 μg
Limit of Detection = < 0.04 μg/filter		
*All area samples were taken operator side of the glove bag.		

Table B. Summary of area and personal sample air concentration data ($\mu g/m^3$) for single cartridge filter housing.

Baseline Risk Identification of Ergonomic Factors (BRIEF™) Risk assessment of the unit operation - filter change out

The BRIEF™ survey is a risk evaluation method using a structured and formalized rating system to identify ergonomic acceptability on a task by task basis.

Results

Containment Capability Study Results

See Tables A, B, and C, and Figure 3.

Ergonomic Assessment Results

Anthropometric Data

For the purpose of this assessment, the filter housing unit was positioned upon a standard table.

- height of table (top) from floor level = 715mm
- height from table top to top of filter housing = 570mm
- height at which filter housing is opened = 460mm (from top of table)
- working height, i.e., from floor to bottom of elbow = 1170mm

Ergonomic Considerations with Regard to Glove Bag Use

Glove Bag Positioning

The glove bag is suspended from a fixed point by use of flexible supports which allow movement of the bag. The height at which the glove bag is placed is ultimately dependent on the fixed position/location of the filter housing which will vary in industry.

Glove bags are purpose designed for specific pieces of equipment and the operations that must take place. The specific aim of the design is to allow the operation to take place in a contained system, which also is user friendly.

The glove bag sleeves are positioned at the height of the operation (through raising/lowering the bag using the flexible supports). The glove sleeve oval is 330mm in diameter with size 10 gloves fitted as standard. Glove sizes can be changed to suit the user population, e.g., a predominantly female population who may require a smaller glove size.

The efficacy of the glove bag in accommodating all users is dependent ultimately on the positioning of the filter housing unit and any obstructions in the vicinity, e.g., if the filter housing is positioned, e.g., at floor level or above elbow level, providing a comfortable working position may not be possible even with the use of the glove bag. Having to operate with arms in a raised position (i.e., above elbow height level) places a significant level of strain on the person, even for short periods of time). If squatting or kneeling are required, static loading on the muscles or joints of the legs will occur.

Glove Bag Operations

The glove bag is designed to accommodate the operations that must take place at the particular piece of equipment. This design takes into account the range of tools that must be used. The size of the glove sleeves, i.e., diameter will take account of the tool/filter dimensions, the length of the glove sleeves will be determined by the operational constraints.

Glove Bag – Additional Features

A HEPA filter is in place on all bags, minimizing any problems with condensation developing during the operation. The material of construction allows full visibility to the user.

Manual Handling Risk Assessment Results

The following two manual handling operations were assessed:

1. lifting off filter housing lid
2. removing/replacing filters

Both tasks were classified as low risk. The use of the glove bag when completing the manual handling tasks did not pose any additional ergonomic difficulties to the operator.

BRIEF™ Risk Assessment Results

The BRIEF™ risk assessment findings of the operation subtasks did identify a number of high risk hand positions; however, these operations are related to the filter housing system and not related to the glove bag use per se. The use of the glove sleeves may affect operations by slightly decreasing

Figure 4. Inserting a new filter into a single cartridge unit using glove bag design.

operator dexterity. The operator may need to increase the grip strength used because of the use of the gloves.

Discussion of Results

Discussion of Containment Capability Results

Table A shows a summary of the lactose air concentration data (mg/m^3) obtained for area and personal samples when using the closed system glove bag design on the five cartridge filter housing unit. All personal samples were non detectable (<0.04 mg /filter). Most of the area data also was non detectable (<0.04 mg /filter), the average area concentration during the unit operation sampled was 0.042 mg/m^3. Detectable data obtained for area samples during background sampling post trial one and pre trial two and during trial two and trial six were both less than 1mg/m^3. Post trial one a small leak (< 5mls) was observed at the connection point of the circulation line and the pump. The leak was dried and the area was covered for the remainder of the test. Detectable lactose concentrations are attributed to this leak and not failure of the glove bag containment features.

Table B shows the area and personal lactose air concentration data (mg/m^3) sampled during the unit operation using the glove bag design with the passive 'feed in' airlock and detachable 'waste disposal' sleeve on the single cartridge filter housing unit. All area and personal data was non detectable (<0.04 mg /filter).

Table C shows a summary of the lactose air concentration data for the cartridge filter removal task without the use of a glove bag. An average air concentration value of 308.5 mg/m^3 and 1535 mg/m^3 was obtained for the task filter removal from the five cartridge filter housing unit post wet filtration and from the single cartridge filter housing unit post dry filtration respectively.

A comparison between lactose air concentration data obtained for the task filter removal from either the single or five cartridge housing unit with and without the glove bag clearly shows a reduction in lactose air concentration of up to 1000 fold for this task when using the glove bag,

Figure 3 is a plot of particle counts during the dry powder trials versus the background counts before each of the trials. The solid line on the graph is a linear regression line with a slope of unity, which indicates that particle counts in the room during the trials did not exceed baseline counts. A similar pattern was observed during the wet filtration trials (data not shown). In each case, particle counts for respective size cut-off diameters of 0.3 mm, 0.5 mm, 0.7 mm, 1.0 mm, and 5mm were recorded.

Discussion of Ergonomic Results

Completing this task (using glove bag technology) should not present any serious ergonomic risks in the workplace if the filter-housing unit is positioned at a suitable working height and there are no obstructions for the user to deal with, e.g., lack of overhead space etc. In order to provide adequate clearance, the workstation should allow 2030mm from floor to ceiling to accommodate all workers. A standing work position is suitable for this task, as the duration is relatively short. If necessary, a sit/stand option could be provided.

Use of a fixed glove box to provide containment for this operation may be an option. However, there are a number of ergonomic disadvantages associated with the use of fixed containment methods, i.e., the structure and positioning of the unit is fixed. While efforts may be made to accommodate the majority of users, it is not possible to suit all users. Persons in the fifth percentile (i.e., smallest members of the population) and the 95th percentile (i.e., tallest/largest members of the population) may be at risk. The working height at which the structure is positioned and the reach distances allowed by the glove portals also are fixed.

Working in glove boxes requires extended static loading on the shoulders. Extending the arms for more than a couple of minutes can become very tiring.[7] Grip strength is reduced when gloves are worn.[8] Therefore, the glove box user may have to overcompensate on grip strength.[7] It must be noted that most ergonomic problems associated with glove box use are related to the extended nature of glove box operations, and the static loading that occurs at the shoulders. However, the task studied in the present work is very short in duration

Location Title	Number of Samples	Average Result (μg/m3)
Filter removal from 2 cartridge filter housing unit (post wet filtration)	3	308.5
Filter removal from 5 cartridge filter housing unit (post dry filtration)	3	1535.0
Limit of Detection = < 0.04 μg/filter		

Table C. Summary of exposure data (μg/m^3) for filter removal from the single and the five cartridge filter housing without the use of a glove bag.

and would not have the same ergonomic risk.

The user friendly/ergonomic advantages associated with the use of the glove bag include:

- The height of the glove bag can be raised/lowered to suit the user.
- The user can be positioned as close as is necessary to the equipment in order to complete the operation, as there are no fixed constraints.
- The glove bag hand ovals can accommodate all users, as the reach requirements are not fixed due to any physical constraints. The bag moves with the person, and the glove sleeves can accommodate all arm sizes.
- Glove bags are a cost effective option for retro-fitting older plants and equipment, as they are purpose designed for the piece of equipment and the task requirements.

Conclusion

The lactose containment capability air concentration data (mg/m^3) demonstrates that both glove bag designs, the closed system, and the design with the passive 'airlock' and 'disposal sleeve', are capable of containing the placebo material to < $1\mu g/m^3$. When comparing air concentration data collected for the task filter removal from either filter housing, with and without the use of a glove bag, a significant reduction in lactose air concentration is observed when using the glove bag. The containment capability study concludes that both glove bag designs could be used as an engineering control in workplace situations where containment criteria of 1 $\mu g/m^3$ are required. However, it is recommended that an in-house containment capability study be completed using the material for which the system is intended to contain before use. Future work also should include surface swabs to assess the surface contamination surrounding the unit, and address dermal risk.

The glove bag design allowed the operation to be completed unhindered and is considered a suitable (ergonomically friendly) alternative to glove boxes, dry break coupling, or use of PPE. The glove bag use allows for a range of adjustability, where the needs of a large group of people can be accommodated; therefore, it is a cost effective method of design.

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Laboratory Instrument Qualification: Solving the Puzzle

by Jason C. Fitz

This article presents the process of qualifying laboratory instruments. It provides documentation needs, categorization suggestions, testing approaches, and resource requirements necessary for a successful program. The article begins with instrument design and purchasing, covers installing and qualifying, and discusses the support systems that maintain the instrument in a qualified state throughout its life.

Introduction

Bring up the topic of laboratory instrument qualification with your colleagues, and notice how quickly they develop a puzzled look. This is ironic since lab instrument qualification is nothing new; it contains a very familiar word, qualification. A familiar word from the manufacturing equipment realm. An instrument is a type of equipment, whether it is used for manufacturing, packaging, or laboratory purposes. It has to be installed, requires external utilities for it to work, and people to operate it. Granted, there are inherent differences between the two, but the approach to equipment qualification and instrument qualification is quite similar.

Where to begin?

Developing a strong instrument qualification program begins with understanding qualification. Qualification is using an efficient and science-based approach to provide documented evidence that the instrument is capable of consistently operating within established limits and tolerances for its intended purpose while being properly maintained and calibrated.[4] This not only serves to meet the FDA requirements, which call for companies to establish procedures to ensure fitness for use of instruments that generate data which support product testing, but also enables the everyday lab objective of consistently obtaining reliable and valid data to be satisfied. Examples of these requirements can be found in the following 21 CFR parts mentioning instrument and equipment: Part 211.160b4, 58 Subpart D, 58.6, 58.63/a, b, 211.63, 211.65a/b.

In order to fulfill these requirements, a process is developed and followed, and like any-

Figure 1. Critical documents.

thing in this regulated industry, it begins with documentation. Do not overproduce documentation though. It is of critical importance to stay focused on the scientific value of the process and not get lost in producing documentation.

A way to stay focused, and to keep the documentation simple, is to create an instrument history file. Take a folder, label it, and add the relevant documentation. Include purchase orders, repair records, calibration records, maintenance records, etc. The file helps to track and categorize the different types of instruments, and eventually serves as the foundation of the qualification.

The Master Plan

Now that the file system is compiled, it is time to use the information it contains. Begin by developing a Master Plan (MP). This is a high-level document that generally discusses the company, the lab site, its operations, and internal processes. The document identifies the key members who oversee and participate in the process, along with their responsibilities. The scope of the document is defined and any limitations and exclusions are captured since there are times when certain items are covered by other plans, i.e., if a lab decided to split computer systems validation and instrument qualification. The MP states the basic process for qualification, including a general discussion of development, execution, review, and approval. A list of instruments (this can be developed from the history files), required resources, and a timeline for the different phases of completion are included. Since the instrument list and timeline are dynamic, ensure the MP is flexible to allow for constant changes. Evaluate this overall program periodically to ensure that current regulations and requirements are met and excessive or inefficient practices are eliminated.

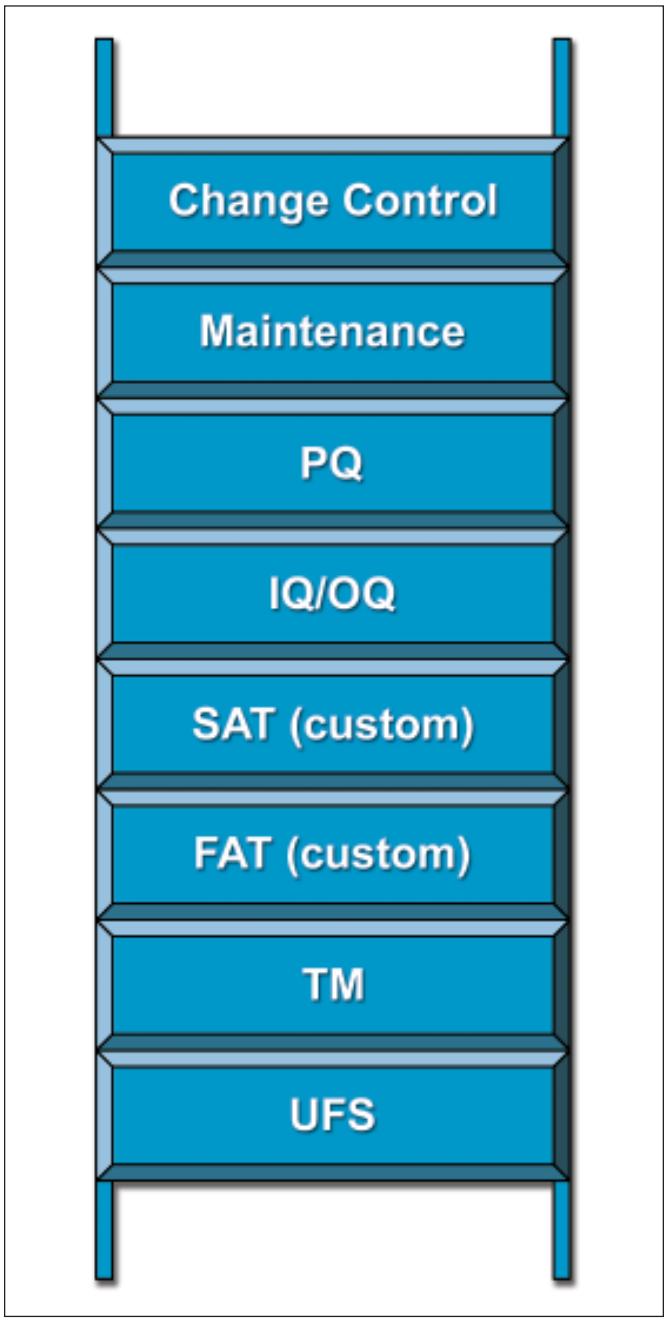

Figure 2. Climbing the instrument qualification ladder.

Since there are numerous types of laboratory instrumentation, they are classified to determine the extent (if any) of qualification. There are numerous schools of thought on how to classify an instrument for qualification. An excellent resource commonly used for this matter is the ISPE Baseline® Guide for Commissioning and Qualification,[7] which helps with determining what requires qualification and what does not. This document provides guidance for assessing the impact of a system. By understanding how the instrument operates, the data it is intended to produce, and deciding if the instrument has a direct impact on product quality, the need for qualification is determined.

Since there are most likely numerous instruments in a company's laboratory, this can result in a timely process that can affect the development of the Master Plan and associated timeline and resource planning. This initial issue during the planning phase can be resolved by using a simple categorization of instruments. This also will provide a solid understanding of the extent of qualification activities required for the instrument. Then, once an impact assessment of the instrument is conducted, the impact on product quality is determined and the extent of the qualification is solidified. The Master Plan, associated timeline and resource planning can then be updated if required.

Any number of categories can be selected for this matter, as long as they are defined with solid parameters, but it usually comes down to this simple Lab Qualification Trident:

First Prong - Preparation

General service equipment not used for making measurements or with minimal influence on measurements, such as stirrers, certain volumetric equipment, glassware, hot plates. Qualification is most likely not necessary. Just ensuring they are correctly used, maintained, and are suitable for the testing and their environment usually suffices.[5]

Second Prong - Measurement

Simple equipment that is used to perform measurements

affecting test data. These instruments have an operating procedure and are usually stand alone while producing one type of datum. Qualify these instruments based on their normal use and standard operating procedures. These include incubators, pH meters, ovens, viscometers, and balances.

Third Prong - Complex Analysis Systems

Complex and highly method specific instruments that require extensive setup and operation, and produce a variety of data. These are usually dependent on other instruments and systems based, and/or require computer interaction for data processing. Examples include HPLCs, GCs, MS/LC, AA, dissolution baths.

People and Procedures

Now that the MP is assembled, it is time to think specifics. A more detailed Standard Operating Procedure (SOP), or set of SOPs, is developed that describes the overall qualification process. The procedure includes the areas involved, the identification and tracking of documents, required protocol content, the approval process, qualification performance steps, re-qualification parameters, and supporting program references (these will be discussed later).

After the SOP(s) is developed, it becomes quite evident that the qualification program cannot be handled by any one individual. It requires a team effort to ensure proper and timely execution, and to obtain a well-represented company view. Select this team from the departments identified in the MP. The team should include, at a minimum, representatives from the user department, quality, and validation. Other departments include engineering, calibration, instrument services, and information technology. The team is responsible for reviewing and approving the protocols for their respective areas of expertise. In addition, they discuss deviations, corrective and preventive actions, procedure development, instrument scope and changes, resource requirements, and any other qualification related topics.

Beginning the Qualification Process

The first responsibility of the team is instrument selection. This decision phase is commonly referred to as Design Qualification (DQ), a familiar process that all companies complete before purchasing an item. The DQ ensures the process has the right people involved, covers all aspects related to the instrument to make sure the correct one is purchased, and documents the activities. The goal is to ensure the selected instrument is fit for its intended purpose.[1]

Before investigating what instrument to purchase, identify the instrument type. A document called the User and Functional Specifications (UFS) is developed to capture what the user needs the equipment to do. In the UFS, the basic functional requirements outlining the key features are defined. Such things as the environment it will reside in, the operating range it will cover, how often it will be used, type of analysis technique, the types of materials it will test, local/federal regulations it must satisfy, safety and utility requirements, procedures for operation, maintenance, calibration, computer interaction, and user interface friendliness are captured. The key here is to describe exactly what is needed so the instrument does not end up being inefficient. It is a good idea to discuss the operating range requirements and tolerances with the team, and if the same instrumentation was used for method development, extend it to R&D. (This should have been handled during method transfer, but communication is not always open so involve them.) By utilizing the expertise on the team, it is likely that most of the UFS can be selected. If there are cases where the team is not certain, contact a reputable vendor and obtain their input. Do not hesitate to even contact colleagues in the industry who have experience with the instrument in question.

Item	UFS	IQ	OQ	PQ
Document ID	UFS-06-014	IQ-06-033-01	OQ-06-028-01	Not Developed Yet
1.0	Instrument read to 3 decimal places	NA	Section 8.2 Test 4	
1.1	Instrument rounds to 3rd decimal place, does not truncate	NA NA	Section 8.2 Test 5	
2.0	Instrument requires password to change alarm fault level	NA	Section 8.3 Test 7	
3.0	Instrument displays version upon startup	Section 7.3 Test 4	NA	

Table A. Traceability matrix (off the shelf system).

Once the UFS is developed, the next step is to create the Traceability Matrix (TM), which makes the qualification process more efficient and controlled. The TM is a simple concept that enables each UFS item to be linked to each document produced during the qualification process, verifying the requirements were satisfied. The idea is to create a simple grid that contains the UFS on the left side (uniquely identified) and the remaining documents (i.e., SAT, FAT, IQ, OQ, etc.) to be produced running across the top row. This document changes constantly based on requirement changes and document development.

Instrument Selection

Now that the initial documentation is in order, it is time to

Figure 3. Instrument qualification support programs.

build or choose the system. Select a number of vendors who manufacture the type of instrument defined. Besides ensuring the vendor has an instrument that meets the UFRS, ensure they have the necessary quality systems in place to develop, manufacture, and test the equipment.

This is done by auditing. There are two types of auditing practices to follow depending on the type of instrument. If the instrument is Off The Shelf (OTS) and familiar to the industry, an abbreviated audit is conducted. A basic questionnaire or checklist can be used to verify the vendors' quality. Obtain documentation from the vendor to serve as proof of their ability to build a quality instrument. Investigate the companies reputation, talk to others who have interacted with the vendor for their opinion and experience, and check to see if they are certified by a recognized agency, such as ISO. Verifying basic standards like these assures the quality is there. If someone else has done the work, why do it again.

On the other hand, if the instrument is custom built or the vendor does not have a reputable history, a full on-site audit is needed. Assuring the vendor has the quality systems in place will ensure the equipment you receive works properly, lasts, and has the support needed. Ensure the company process for a detailed audit is completed; ensuring evidence that the vendor meets the company's requirements for the quality systems are documented.

Besides ensuring the quality systems are in place, one of the most important and often overlooked items is support. What does the vendor offer in addition to just building the equipment? They are the experts and already have documentation of testing that has been conducted on the equipment. Make sure they will allow document copies, because it serves as documented evidence for the DQ that the equipment is designed correctly, and also may serve as a development tool for the Installation/Operational Qualification (IQ/OQ), or documentation to satisfy IQ/OQ requirements.

The vendor also should develop or assist in the development of operation, maintenance, and calibration procedures. They know best how the instrument operates and can provide the necessary training, which is always critical, off and onsite. Ask what type of installation trouble shooting support is provided as well. All of this affects the funding requirements during the qualification and lifetime use of the instrument. Ensure these are discussed and more importantly documented so that the reasons behind the vendor selection are known.

Discuss the user requirements with the responsible areas and further detail and develop the specifications for the instrument prior to purchase. When the vendor proposes a design to satisfy all of the user requirements, review the proposed instrument to ensure the instrument's function will satisfy the requirements. This cycle is repeated until the vendor's instrument design suits each item of the UFS.

Once the instrument design is accepted (for custom built systems, not OTS systems), it's time to test it. Develop a test protocol with the vendor to ensure all company requirements are met, and all necessary documentation will be included and turned over by the vendor upon completion of the protocol. It is likely that the information gathered from completing this protocol will be used to support or eliminate certain testing during the IQ/OQ phase. For example, if there is Radio Frequency (RF) or Electromagnetic (EM) interference, testing to ensure RF and EM do not affect the operation of the equipment when in close proximity should be complete. Once performed here, there is no need to re-verify it during the IQ/OQ phase. This protocol that is executed with the vendor at their site is commonly referred to as the Factory Acceptance Test (FAT). Although OTS systems do not require FAT, there most likely is relevant testing documentation that the vendor has accumulated during their development phase for the instrument. This documentation can serve as a source for test step development and acceptance criteria during IQ/OQ testing. Therefore, it is wise to gather this information from the vendor at this time.

Once everything is approved and in order, instrument delivery is scheduled. Prepare the area in your facility for delivery and installation. Ensure the physical dimensions of the instrument can be accommodated, and the correct utilities and support systems are available. Once the instrument arrives, basic checks can be performed to ensure nothing happened during shipping and the equipment is what was

Step	Expected Result	Actual Result	Pass/Fail	By/Date
1. Ensure the pH Meter is connected to a power source and turn the power switch to the ON position.	Display read "pH Meter", then changes to "Version 2.2", then changes to "Diagnosis Check..."			
2. Allow diagnosis check to complete	Diagnosis check completes and display "Diagnosis Pass", then changes to pH display			
3. Insert the probe into the 4.0, 25.0C buffer solution and press Calibrate	Display reads "Select buffer"			
4. Enter 4.0	"4.0" displayed, then beeps and displays "Enter buffer"			
5. Remove probe, rinse with DI Water and place in 7.0, 25.0C buffer and enter 7.0	"7.0" displayed, then beeps and displays "Test sample"			
6. Remove probe, rinse with DI Water and place in prepared 5.5 standard sample	Displays 5.50 (+/- 0.02) and slope of 95-105%	pH = Slope =		

Table B. pH meter operation test example.

ordered. This is commonly referred to as the Site Acceptance Test (SAT) for custom built systems.

As the instrument arrives on-site, create the Instrument History File and add it to the instrument tracking database. Ensure the equipment is assigned an ID number via the instrument identification system and a corresponding logbook. Do not stop at updating the inventory system, update the Preventative Maintenance (PM), calibration, and other support systems as well.

Installation and Operation Qualification

Now that the instrument is on-site and set-up in its correct location, it is time to test if this instrument does what it claims to do. How? The answer is Installation and Operation Qualification, or IQ/OQ. IQ and OQ are usually combined since they can be executed together and have testing that can be applied to either one. There are many guides and opinions of where selected testing belongs. Remember, it's not so important where the test is placed in the protocol, just that the correct test is there.

There is a very useful document for developing IQ/OQs. A template is a fantastic concept that ensures that the basic requirements from company procedures and standards are always satisfied; increases the efficiency of the development; and reduces the chances of deviations or missing tests. A particular caution arises when using templates. A template is a dynamic guide that is not set in stone. There will be sections of testing that apply to certain instruments, but not to others. Therefore, be sure to remove unnecessary sections or document the rationale why they are not being performed.

The following sections should be included in the template: the purpose of the qualification effort; what the qualification is applicable to; area roles and responsibilities; instrument description; associated procedure and reference documents; and most important the IQ and OQ sections. This template then becomes the foundation of every instrument protocol. This can be quite a large number so it is important to create a unique ID system for the protocols and the associated instrument. This prevents confusion and mix-ups, and allows for tracking and retrieval at any point during its lifetime.

The first decision when developing the protocol is to decide if an individual or group approach will be taken. This occurs when the system is made up of a group of components/instruments that undergo separate qualifications. Usually they are IQ/OQd individually and Performance Qualified (PQd) as a group; however, the group approach can be for IQ/OQ as well. This approach has the same testing structure as an individual, but applies it to the actual systems verifying the operation of each component while testing the impact they have on each other and the overall system.

Within the body of the protocol, discuss if the system is existing or new; portable or stationary; and its user range. All equipment has an operating range, but this is not necessarily the user range, which is the range that the instrument is operated over. Take a pH meter as an example. If the range is 0 to 14, and sample testing is only conducted from 5 to 9, qualify a range that brackets those numbers, i.e., 4 to 10.

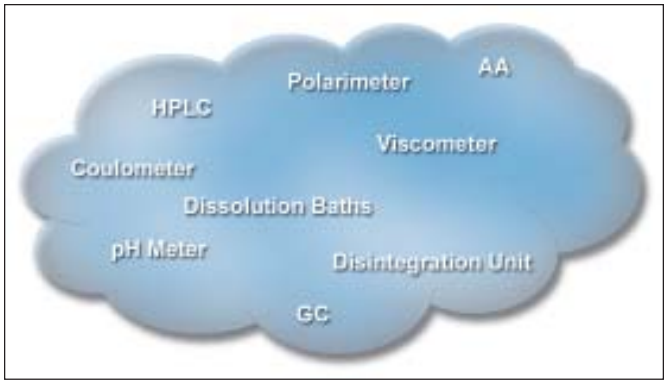

Figure 4. Typical instruments for qualification.

Also, just because a piece of equipment can perform more than 100 different functions, does not mean they all have to be qualified. Investigate the SOPs, test methods, and other pertinent documentation to determine which functions are used, and what the range of use of the equipment is. Limit the testing to these parameters since they are the critical ones. Testing additional functions is allowed of course, but it can lead to unnecessary deviations, work, and resource allocation.

With all the information assembled, the IQ and OQ can be developed. The IQ is used to ensure that the instrument has been installed properly. It verifies all of the equipment is present and received as designed and specified, properly installed, and that the environment is suitable for the instrument's operation. It is quite a simple process that requires document collection and set-up verification.

Begin with checking the order against what was actually delivered. Examples include tools, parts, procedures, manuals, purchase orders, certification/calibration records, and drawings. Inspect the actual instrument for any damage that could have occurred during shipping. Locate and record identification information such as the manufacturer, model, and serial number.

Connect the required support utilities, the accessories and components, and verify that the connections and flows are set properly. Utilities can include nitrogen, compressed air, water, electricity, temperature and humidity controls. There are certain instruments for which the environment parameters are very critical for operation. A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.[4] If the activities are critical to the operation of the equipment, then verify the range. As will be discussed, the OQ actually verifies that the instrument operates as intended in the selected environment.

Once the instrument is hooked up, it is time to power up. Check that it boots up properly and performs any initial diagnostic checks. Refer to the corresponding instrument documentation for what is supposed to be displayed and confirmed by the instrument, and verify this in the protocol. These instruments, as well as many others, have some form of computer control that is critical to the operation of the

instrument. Verify that the correct versions of the firmware/software are installed. If possible, produce a back-up copy. It is always good to have this on hand in case some malfunction occurs that requires reinstallation of the program.

Include verifying network connections and data storage. This is entering the realm of computer systems validation, which is a topic separate from this article. During MP development, the decision to keep computer validation in the MP or to develop a separate MP was made.

Assemble and keep a record of all of the associated documents. This includes what was initially checked for upon delivery, the vendor manuals, purchase orders, contracts, etc., and those documents that may require development, such as cleaning, calibration, and maintenance SOPs. Some critical items to consider are the recommended instrument service and its interval, the qualification interval if any, the consumables required for normal operation of the instrument, and the start up and shut down processes. It is very likely that the internal procedures are only in the draft phase at this time. This is fine. In fact, during the IQ is when these procedures should be verified to be written correctly. Walk through each step of the procedure ensuring it follows the operation of the instrument and the user's needs correctly. Any modifications that are discovered should be documented, and the changes approved through the company document approval cycle. It is good practice to have the documents in final format approved and signed prior to completion of the protocol summary report. This ensures approved materials are available to ensure the proper training can be conducted before the instrument is in everyday operation.

Instrument operation today usually requires the assistance of associated smaller instruments, some of which may require calibration. List these. Take the GC as an example. This instrument may have a controlled temperature environment for the column and for the sample. It also can have pressure gauges for the corresponding gases. These associated instruments play critical roles in controlling the key factors of pressure and temperature operation of the instrument. It is of critical importance that these instruments are calibrated since they affect the execution and validity of the testing and data. If they are not performing correctly, neither is the equipment. Also, include test tools and their corresponding calibration certificates that will be used during the qualification; such as thermometers, multimeters, and micrometers for temperature, voltage, and measurements verification respectively.

Something that is often overlooked is lubricants, filters, and Material of Construction (MOC). Filters and lubricants are not only required for the proper operation, but they may affect the results produced if they end up contaminating the sample. This is true for the MOC as well. Even though the instrument surfaces do not come in contact with marketed product, there are surfaces that do come in contact with the sample. This should have been thought of during the DQ phase, but during IQ, the actual materials are recorded ensuring they do not add to, absorb, or decay the sample.

Just as the IQ ends, the OQ begins. Operation Qualification (OQ) is demonstrating that an instrument is appropriate for its intended use by documenting that it performs according to the operating specifications in its selected environment. It tests the functions of the instrument that were defined in the UFS over the user defined operation range. There are different functions of OQ that affect the selection of testing. As with anything, it boils down to selecting the test based on science, and if it adds to the quality of the instrument/process. Remember, the ultimate goal is to prove the instrument provides valid data.[4] Focus on selecting those important parameters for testing according to the instruments' intended use.

Begin the OQ by documenting any additional equipment that is needed to properly perform the testing. This ancillary equipment must function properly itself since it interacts with the equipment and affects the results. For instance, if a water bath is required to keep a sample at 25°C during testing of a Viscometer. Since viscosity results are dependent on sample temperature, the water bath becomes a critical component of the testing.

If the instrument has security features that protect critical parameters that affect the outcome of the data, challenge them. There is nothing worse than having someone change a parameter they shouldn't have and end up with failing test results due to it. Take for example a Melting Point Apparatus. Units have temperature and gradient (temperature increase over time) parameters that can be chosen. Since these parameters are used to determine the final outcome, they are critical. When the unit has a security measure protecting these from being change by an unauthorized individual, testing is necessary. There may be different levels of access, or just a simple password to protect the parameters from being changed. Include testing for attempting to access the different parameters, both with the correct and incorrect user ID/passwords. Again, only test those features that are used to protect these critical parameters. Do not test what is not used or not necessary.

Alarms are common features that warn the user of invalid operation, failing results, or excessive conditions. Exercise the instrument to produce the required conditions to trigger the alarms. This can be done via actual operation (setting the alarm below or above the current reading) or simulating alarm conditions (using a signal generator). Either way, document how the alarm is triggered, what happens when the limit is met, and how to extinguish the alarm and bring the instrument back to normal operation.

If there are critical settings and/or data that are stored, verify their status following a loss of power. Do they retain the settings/data; is a reset required before operation continues? If a procedure covering handling a loss of power is in existence, then this section is satisfied. If one does not exist, perform adequate testing to ensure the parameter settings behave as expected. This is a good place to check for secured data storage, and backup and archival abilities. These are usually part of computer validation, but walk a fine line and can be included here.

All instruments are controlled by the user in one form or

"Whatever the ranges, following the completion of the final qualification protocol (whether it is Installation, Operational, or Performance), label the equipment as qualified."

another, and this is usually done via a keypad or set of control buttons. Call this Operator Interface Testing (OIT). Since this operator interface is critical, test the functions of the buttons, knobs, keys, and how they interact with the instrument operation. Define and test the action, how to select it, and what happens when it is selected.

Now that the different functions and items of the instrument are tested, it is time to test the instrument as an entity during normal operation. Call this Sequence Testing. Utilize the standard operating procedure and run through its sequence, verifying the instrument operates as expected during an everyday routine use. Be sure to document any standards or samples used to simulate actual work conditions and be sure they are valid.

Be sure to conduct sample testing over the range that is being qualified. Run samples of known value to challenge the accuracy and response of the instrument. Different equipment has different specifications, depending on the manufacturer and type of test. The USP, EP, and JP are excellent sources of information on development of certain acceptance criteria for accuracy, etc., so refer to them.

Many people ask if a calibration or verification check is needed during qualification. It can be done of course, but since it is conducted on a routine basis, repeating it in the qualification does not add to the quality of the testing. Either way, ensure the instrument is in a calibrated state prior to qualification. This goes for the PM status as well.

Remember, like calibration, there may be instances when the qualified range is deemed limited, or when a limited testing range verifies a larger qualified operating range. Whatever the ranges, following the completion of the final qualification protocol (whether it is Installation, Operational, or Performance), label the equipment as qualified. If the instrument is limited to a certain range, document it on the label.

With all that going on in the IQ and OQ, there are a couple of key items to remember during execution. Document the samples, standards, and reagents that are used and provide documentation for the quality status of these materials. It is critical that they meet the requirements set forth by the company, regulatory bodies and agencies, such as NIST, and the manufacturer's own specifications.

Instrument	Re-Qualification/ Additional Testing	No Re-Qualification/ Additional Testing
pH Meter	Change software	Replace probe
Disintegration Unit	Replace bath heater and circulation system	Replace beaker
HPLC	Change Detector	Replace Lamp

Table C. Changes requiring RQ.

Performance Qualification

Now that IQ/OQ is completed, it is time to decide if PQ is necessary. PQ is verifying a set of different components that have been IQ/OQd perform as expected when operated as a whole to perform a specific method/process. PQ ties directly back to the UFS, confirming that the instrument consistently performs according to specification appropriate for its routine use. PQ and OQ sound quite similar. When thinking of PQ and OQ, remember PQ (validation) is application orientated and relates to a specific measurement, method, or process, whereas OQ (qualification) is instrument orientated and relates primarily to the operational spec of the instrument.

An approach besides or in addition to a PQ Protocol for routine verification of operation and qualification status (i.e., yearly) is developing an SOP that is performed on a routine basis. This is developed to check the performance of the equipment through a series of checks and tests using parameters as close as possible to those used during normal routine operation of the instrument. This also is known as performance verification.

Another approach is to verify the different test methods that are used with the instrument. This is similar to the Sequence Testing in OQ, but focuses on specific methods as opposed to routine operation. If an HPLC is used to test for active ingredient levels in a allergy product, OQ would apply to testing instrument operation as it applies to any allergy product A, B, or C, where PQ would verify the specific setup and operating parameters of the test method for just product A. This verifies that the instrument performs as expected when using different materials, parameters, and solutions. Many times this is covered under Method Validation, but it can be extended to a periodic test to ensure the instrument is still operating properly. It all comes back to what is stated in the MP.

Once the equipment is qualified, summarize the qualification and have it approved by the Qualification Team members, and release the equipment back into service via the appropriate route with an ID tag of its qualification status.

Good Things Come in 'Vendor' Packages?

What happens if the vendor has a qualification package? Well, it definitely can be used if it fits the users' needs. The vendors are the experts on the instrument, for now, so their protocol should be solid. They use these protocols for numerous clients so they have been tried and tested true. The only thing is it will be generic. An internal protocol should still be developed to capture any missing requirements that the company has and to ensure the document is controlled. Also,

keep in mind that the vendor protocols will usually require vendor execution. Ensure they are properly trained and fully aware of internal procedures and processes. If not, it can lead to deviations and a large amount of downtime and wasted resources. It is advisable to accompany them when completing the first execution.

Is it Over?

Now that the instrument is qualified, it does not have to be touched again, right? Wrong. There may be a time when a change is made that requires Re-Qualification (RQ). Different circumstances include movement or relocation of a stationary instrument, interruption to service or utilities, routine maintenance and replacement of parts, instrument modification, and even change of use.[2]

Changes

In order to recognize a need for RQ based on these different circumstances, the Control program plays a major factor. Changes are evaluated for the impact they have on the instrument, the process, and the product. The change control program ensures the change is discussed prior to implementation, the right resources are assigned, proper testing is conducted, and documentation approval exists and is maintained. The required testing may include repeat of IQ/OQ activities, new testing, or other process/documentation modifications. The program maintains the qualified status of the instrument, thus continuously monitoring the instrument for RQ. Major changes are likely to cause a need for RQ, but minor changes most likely will not. This is why it is important to review the instrument history files each time a change control is initiated. This way the history can be analyzed and a determination made if the qualification status has changed and RQ is required. Also, remember our discussion on PQ…If the PQ is done periodically, it is confirming that the minor changes made are not affecting the qualification status of the equipment and its ability to produce valid data.

As noticed with Change Control, Qualification is dependent on other programs. In addition to the change control program, other support systems are required for a valid qualification program. These systems also add to the support of consistent and constant performance verification.

Additional Support

Training

Training ensures proper instrument operation and that the process for producing quality data is always followed. Training associated with the protocol, the setup and operation, maintenance, cleaning, and laboratory practices are all critical, for both employees and vendors/contractors. Records are maintained and only trained personnel are allowed to interact with the instrument.

Preventative Maintenance (PM)

A strong PM program sets the frequency of maintenance conducted to ensure the equipment does not encounter unnecessary breakdowns or stoppages while sustaining the life expectancy of the instrument. Maintenance intervals are defined, documented, and an integral part of the qualification life cycle.

Calibration

Calibration of an instrument ensures when a setting is selected, it produces an outcome meeting that setting. Without this data, validity is questionable. The program for defining frequencies, intervals, document requirements, identification, and operation must be defined.

Deviations

Proper training, maintenance, testing, and utilizing templates are ways of preventing deviations, but error does exist. Deviations add to the timeline so it is important to define them properly. Minor typographical errors, wording issues, cut and paste errors, etc. should be separated from those deviations that could truly pose a critical negative impact to the instrument. Ensuring only the latter types of deviations are investigated will save time and resources without affecting the quality of the qualification.

Auditing

As mentioned previously, auditing your vendors is important. It does not stop there though. The only way to ensure you have a strong qualification program is to perform audits at defined intervals to ensure it is being followed and kept current.

Conclusion

Laboratory Instrumentation Qualification is quite a digestible process. By adhering to this systematic approach, it is guaranteed that the program will be successful and the instrumentation will provide many years of reliable service. By focusing on the science and use of the instrument, the process does not get lost in the unnecessary requirements that companies themselves develop. This keeps it clean, and ensures that quality and valid data are produced by the instruments. So the next time someone brings up Laboratory Instrumentation Qualification, be the first to chime in and be the "answer key" to the puzzle.

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Large-Scale Chromatography Becoming State-of-the-Art

by Roy Greenwald and Bill Rochelle

This article describes the process, design, and fabrication considerations to take into account for large-scale chromatography control and dilution equipment.

Introduction

Over the past five years, the biopharmaceutical industry has seen a steady increase in the size of bioreactors. Whereas in the past it was typical for a large bioreactor to be in a range that might span 3,000 to 6,000 liters, it is not uncommon to now see bioreactors being installed that routinely exceed 10,000 liters and often reach 20,000 liters. Yet, in many installations, the purification process equipment has failed to keep pace or scale up at the same rate. Recently, DECCO Process Solutions (DPS) worked with a large New England biotechnology firm to confront the decision process and engineering challenges related to this scale-up in order to de-bottleneck the typical downstream processing suites. The result of this effort was the design, fabrication, testing, and start-up of the largest biopharmaceutical chromatography skids built by anyone to date. This article describes many of the decision factors, unique design considerations, and challenges that were addressed and overcome in the process.

The manufacturing company recently constructed a new large scale production plant that is a cGMP facility for commercial scale protein and antibody production. Because the cost of biopharmaceutical facilities is often a function of its square footage, it seemed prudent to install as much reactor capacity as possible within the footprint. The new plant was to include three 20,000 liter stirred bioreactors with dedicated seed train reactors. The facility was to operate as a single harvest system.

The next key decision confronted by the

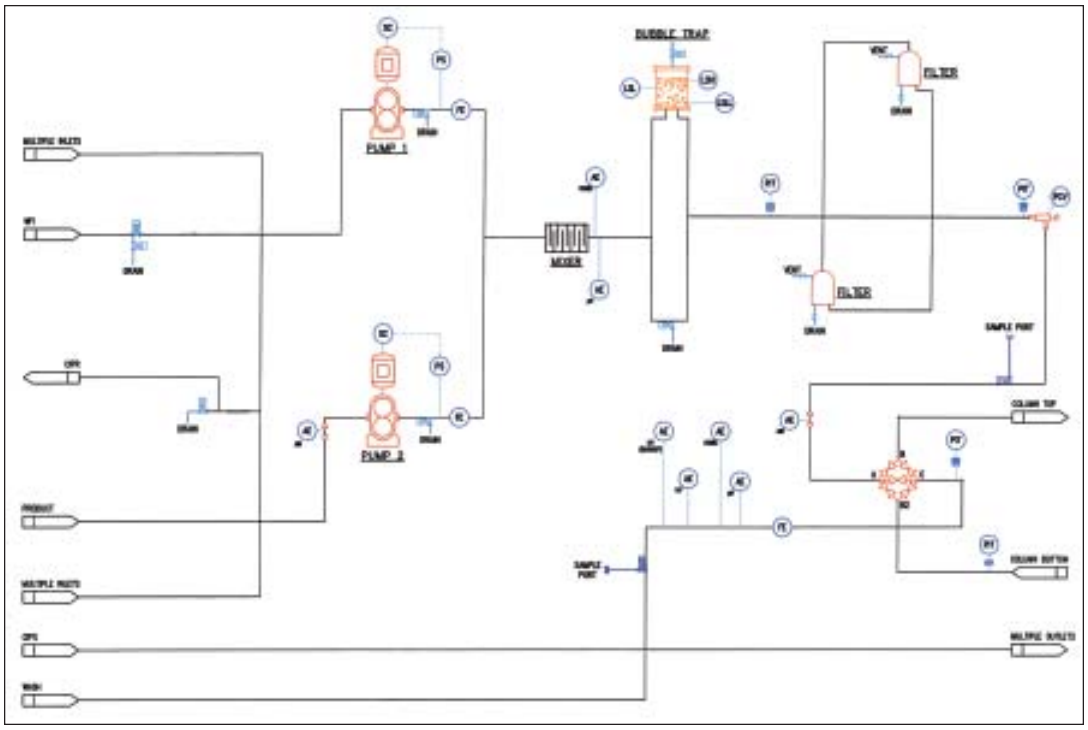

Figure 1. Control and dilution skid P&ID.

	TRAIN 1		TRAINS 2 - 4	
	SI	English	SI	English
Quantity	1	1	3	3
Number of Inlet Manifolds	2	2	2	2
Total Number of Feed Sources	16	16	16	16
Column Diameter Serviced	2 meters	6.6 feet	1.4 and 2 m	4.6 and 6.6 feet
Skid Inlet Line Size	63 cm	2.5 inches	63 cm	2.5 inches
Column Outlet Line Size	50 cm	2.0 inches	50 cm	2.0 inches
Design Pressure	7 bar	101.5 psig	7 bar	101.5 psig
Design Viscosity	1-3 cp	2.4 - 7.3 lb/hr-ft	1-3 cp	2.4 - 7.3 lb/hr-ft
Minimum Flow Rate	5.25 lpm	1.4 gpm	2.6 lpm	0.7 gpm
Maximum Flow Rate	262 lpm	69 gpm	129 lpm	34.2 gpm
Pump Power	11.2 kW	15 hp	7.5 kW	10 hp
Bubble Trap Size	40 liters	10.6 gallons	20 liters	5.3 gallons

Table A. Skid design and physical parameters.

design team was sizing of the purification equipment. In many facilities the purification suites represent the bottleneck in the production stream. The owner decided that would not be the case for their new project. In addition, there was to be a single equipment train dedicated to each specific purification suite. This decision represented a break from the traditional approach, wherein there are often multiple smaller units. As a result of these decisions, the owner worked with their engineering team to produce a performance specification for the largest chromatography control and dilution skids ever built. Table A contains some of the specific variables related to the chromatography skids.

Chromatography Fundamentals

Chromatography has become one of the most frequently employed separation processes in the biopharmaceutical industry due to both the simplicity of its application and its ability to bring high resolution to the separation process. Fundamentally, the chromatography process most commonly selected is based on an ion exchange process that utilizes immobile ligands embedded in an insoluble matrix, packed into a chromatography column. Proteins, polypeptides, and other bio-molecules that are charged, or capable of retaining charge, are suspended in a solute. The solute is routed through the chromatography column under pressure, and based on the interactions of ionic charges may be retained or passed through the column. By changing the conditions within the column, the affinity of the matrix for various product or buffer molecules can be modified. A typical separation process may include several steps in order to produce the required separation. Some studies have indicated that the average number of steps in a biopharmaceutical purification process is four.[1, 2]

As an example, a chromatography column will typically be prepared and packed with the proper matrix media. The "proper" media is based upon characterization studies using a combination of experience, biochemistry, and empirical data. The media itself will have different characteristics, depending upon the product that the user is planning to separate. Normally these characteristics have been established in the laboratory well before production volumes have been anticipated with the purification method validated during FDA clinical trials. The goal in matrix selection, and indeed the operation of the process itself, is to maximize resolution of the separation. The resolution is a mathematically defined parameter that is proportional to three variables: 1. the selectivity of the ion exchange process, 2. the efficiency of the process, and 3. the capacity of the process.[3] Selectivity is influenced by several factors; some are determined by the matrix affinity for particular ions, while some are experimentally determined factors that can be manipulated by the process itself, such as ionic strength and pH. The second parameter, the efficiency of the separation process, is most influenced by diffusion across the matrix bed or channeling through the bed. Ideally, a chromatography column should exhibit characteristics as close as possible to plug flow. Therefore, factors such as bead size of the matrix, packing techniques, air bubbles, and other physical anomalies that can lead to channeling will have a major impact on efficiency. The final factor that influences resolution is the capacity of the process. Capacity is an indication of the ion exchange capability of the matrix which can be influenced by the surface geometry of the ion exchanger. For example, a porous matrix material may allow smaller molecules greater access to surface area than for larger molecules. In addition, the protein's ratio of charge to pH is an important parameter that can be manipulated by the experimental conditions, for instance, via buffer selection, and will influence capacity. Finally, the flow rate through the column has a great impact on capacity. The dynamic capacity of the ion exchanger will normally exhibit an inverse relationship to flow rate, decreasing as the flow rate is increased.

From the preceding paragraph, it can be seen that many of the factors that determine the resolution of an ion exchange

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chromatography separation are inherent in the selection of the matrix. This article will not discuss these areas. However, many of the factors previously noted are determined or influenced by the process and the hardware utilized for the separation process. Most of these must be considered in the selection of the equipment, its design, the control logic, and the operating procedures. These factors do form the basis of this article.

A final consideration that strongly influences the product recovery in a chromatography process is the number of stages, steps, or phases required to collect the product. At each stage, other than initial equilibration, a percentage of the product is lost. As an example, in the most simple of separations, a column might be brought to a set of initial conditions, or a starting state, by pushing a buffer solution through the column at a specified pH and ionic concentration. This buffer will establish an initial set of charged molecules on the surface of the matrix. During the second step, the solute loaded with the product is adsorbed onto the matrix surface, displacing the charged molecules that were loaded via the buffer. The third stage, called elution, changes the conditions within the column so that the product is no longer preferentially bound to the matrix. This is the product collection step. A further step or two may be required to flush the column of undesirable ionic products that remain within the column, followed by a re-establishment of initial conditions. This is the most simple of separations. In most instances, the separation may require additional steps or may involve other complexities, such as gradients, wherein concentrations of buffers vary over time to collect various fractions of samples. This latter technique is often employed in the laboratory to establish optimal separation parameters. The problem inherent in multi-step separations is that even with recoveries of 95% per step, simple math will show that with two, three, or four steps, total recovery would drop to 90, 86, or 81% respectively. Therefore, the abilities of the equipment and control system to minimize losses at each step are critical to effective chromatography system design.

Currently, the supply of the columns themselves, along with their media, is served by a small number of companies. These companies have extensive laboratory and experience bases that allow them to work with biopharmaceutical companies to properly tailor their purification processes. The balancing of recovery, resolution, processing time, and cost is their area of expertise. However, the biopharmaceutical industry also has begun to realize that for Large-Scale systems, the Control and Dilution (C&D) skids should be designed and built by specialty fabricators. This second group of companies has the ability to work closely with the client to design the control of the skid for the specific purpose for which it is intended, and often with a lower cost structure. By necessity, for Large-Scale Chromatography, these are almost always "one of a kind" skids.

Process Design Considerations

One of the design parameters for this project was the ability to purify 20,000 liters of bioreactor output within a set timeframe. In order to process the necessary volume of product, extremely large quantities of dilute buffer were going to be required. There were two options on how to meet this requirement. The first, and obvious one, was to invest in the necessary tank storage needed to inventory the dilute buffers. This would have represented an excessive use of real estate, as well as a large capital investment. The alternative approach was to use concentrated buffer and dilute it on demand on the chromatography C&D skid. This latter approach was the preferred option for the owner's project team. The impact of this decision was multi-faceted. In-line dilution created the following demands:

1. a need for multiple pumps on each skid
2. a need for high turn-down ratios on each pump
3. a need for efficient, but low-impact, mixing on each skid
4. a control system that could quickly and accurately adjust and measure buffer properties

Once in-line dilution is selected as the operational approach for a facility, the C&D skids actually must combine the unit operation of mixing with chromatography control. A failure to recognize this fact may lead to irreconcilable problems in equipment selection and control due to improperly matched pumps, inadequate turndowns, or inability to exercise ad-

Figure 2. Chromatography control and dilution skid – back.

equate control. Another impact of the upsizing of production facilities is that the collection of fractions is usually not practical. This is again due to the size requirements of the hold vessels. Although clinical and characterization studies make extensive use of gradients, Large-Scale Chromatography tends to be for market supply quantities and often finds less application for gradients. This obviously assumes that the characterization studies have been completed and elution phases adequately defined. Typically, flow rates and ratios will be programmed from the two pumps with separate buffer feeds, and blended in-line to create the required gradients. It is also typically necessary to include a backpressure control loop ahead of the column in order to control low flow rates at the low end of the dilution turndown. A typical Large-Scale P&ID is shown in *Figure 1*. This figure indicates hardware requirements, but has omitted the proprietary or confidential control logic.

In accordance with *GAMP® 4* protocols, a User Requirement Specification (URS) was produced to define the owner's needs. This 30-page document included designations of the skid's control boundaries in addition to its physical boundaries. In addition to these baseline parameters, several objectives were outlined. Among these were:

1. ability to continuously perform GMP operations
2. ability to display all monitored equipment variables on-screen, in real-time
3. ability to report faults via a video display and to archive a real-time event log
4. ability to communicate bi-directionally with the plant-wide control system (Delta V)
5. ability to manage both clean-in-place and steam-in-place operations for the skid as defined within the given boundaries
6. ability to produce linear flow rates through the columns of 75 to 500 cm/hr (29.5 to 196.9 in/hr)
7. adherence to ANSI/ISA S88.01 Batch Control Model

Figure 3. Chromatography control and dilution skid – front.

In addition, a further requirement was added as the project evolved, which was the ability to archive and recall "Golden Batch" data for optimized separation runs. This data would be available for use as the baseline of future purification runs of the same product.

Another advantage that most Large-Scale systems present is the ability to work with the owner in a way that integrates the skid into the Plant-Wide Control System (PWCS). In fact, one of the greatest advantages of large-scale systems is that the incremental efforts and cost of PWCS integration is almost always justified. This is another factor that owners cite when making the decision to work with specialty fabricators to meet their needs. Although the smaller chromatography units are often provided by the column suppliers with off-the-shelf expertise in standard programming features, they normally are stand-alone units. The larger systems create an opportunity to interact with hold vessels, CIP, SIP, and other equipment that is not only useful, but provides safeguards as well. As an example of a safeguard that PWCS integration might provide, one might consider a skid flowmeter failure. In such an instance, alternate data collection points can be utilized in real-time (in this case, potentially using buffer tank weigh cells as an input) to calculate loadings to the chromatography columns.

However, the single most important item to recognize regarding the process and automation design of a large scale system is the need to build in flexibility. This is best done by assuring that the data acquisition will be provided by the instrumentation at the required level of accuracy. This must be addressed at the Functional Requirement Specification (FRS) stage. The control system will then be able to produce the necessary routines to allow for the desired level of automation. As an example, it is not unusual that a UV pre-peak might be excluded from collection. This may require incorporating a subroutine to determine the second instance of when d(UV)/dt equals zero to begin collection. Signal data collection, averaging, or manipulation is easily obtained if the initial data is available and accurate; the key is to properly design and instrument the skid initially.

Equipment and Layout Design Considerations

There are many equipment design considerations in the proper design of a Large-Scale Chromatography C&D skid. Although the following list is not all-inclusive, it does contain some of the more critical parameters. The design must address:

- hold-up volume of the skid
- blending instrumentation philosophy and selection
- pump selection, both type and size
- control and elimination of air entrainment
- blending and mixing equipment selection

- cleanability and drainability

Hold-up volume has always been a focal point for chromatography C&D skid owners and designers. This is because every liter lost not only represents concentrated product, but it scales with each separation step. From the previous example, for a 95% efficient, four-step separation (excluding equilibration), if there is a 2% volume loss with each step it will yield a final volume of only 92% of that which one would collect with no losses – that is, 8% additional product loss. Although this is unlikely within the equipment itself, it is possible with a poor equipment design in combination with a poor layout. This is rare in today's production-scale, fully engineered facilities, but may be of more concern in smaller laboratory applications. However, efficient equipment design and full drainability are still essential.

However, hold-up volume actually assumes a decreasing significance in larger chromatography control and dilution skids than in smaller ones. Although this may be counter-intuitive, the reasoning is simple. The ratio of the volume of the skids does not scale linearly with the volume of the bioreactors; it scales more closely with the flow rate through the skids. This flow rate is more related to the dynamics of the entire bioreactor processing cycle with its attendant ramp-up, ramp-down, and non-steady state transients. The goal remains to empty the product tanks quickly, but in a multi-reactor plant there may be adequate down-time between cycles such that the flow rate is set by these other parameters.

Nonetheless, there are several examples of where the flow rate does have a direct impact on hold-up volume. The most obvious of these is the bubbletrap that is typically used to remove entrained gases. A bubble trap is normally sized to provide between 10 and 20 seconds of hold-up volume at maximum flow. Therefore, the bubble trap scales linearly with maximum flow rate (again, not the bioreactor volume). However, because the maximum design flow rate in a larger skid is often not encountered as frequently as it might be on smaller skids, the C&D skid designer has the option of sizing the bubble trap on the lower end of its expected range. These are project-specific decisions.

Another of the large hold-up volumes on the C&D skid appears within the filter housings. These should receive special attention, as the trade-off is often between pressure-drop and hold-up volume. By decreasing filter area and housing size, the hold-up volume is decreased, but other operating factors may become part of the trade-off.

Despite the two equipment items that represent a major portion of hold-up volume, there still remains a significant portion within the tubing and instrumentation. It is noted that for most C&D skids and pump sizes, a standard design velocity is used. Therefore, as the flow rate goes up, only the cross-sectional area of the tubing increases, and it increases with the square of the tubing diameter. Since the velocity is unchanged and the "residence time" in the skid is thus unchanged, one might assume that the volume of the skid would increase linearly with the flow rate. This is close, but not strictly the case for reasons noted previously. In addition,

Figure 4. Chromatography column with C&D skid in the suite.

designers must pay careful attention to fitting dimensions. For instance, by comparing information given in Tables DT-4 and DT-7 of ANSI/ASME BPE-2002,[4] one can conclude that the volume contained in Automatic Tangent Weld (ATW) fittings increases in step increments. Therefore, the volume of a 2" diameter fitting will not be exactly four times that of a 1" fitting, as one might expect. Some C&D skid designers have elected to actually trim the ATW fittings in order to minimize this impact, as this non-linear relationship to the square of tubing diameter can cause larger skids with excessive fittings to trend adversely.

The primary conclusion to be drawn from these facts is that the best technique to minimize hold-up volume losses is to size the throughput accurately and bring additional focus on the volume of the filter housings and bubble trap. However, the percentage of product loss in a large skid, as a function of bioreactor volume, will still usually be significantly less than for a smaller purification train.

For the subject skids, the decision was made to supply all inlets via two separate headers. Header number one had provisions for six buffer feeds and one Water-For-Injection (WFI) feed. Header number two provided for one product inlet, two concentrated buffers, two concentrated NaOH inlets, and three outlets. The valve arrangements on such an assembly can become extremely complicated. If not designed carefully, they also can be a source of much of the non-recoverable hold-up volume as well. Another major factor that is unique to the larger skids is the physical size and weight of the valves themselves. As the valves become larger, the ability to both fit and support the valves becomes more challenging. A careful balance is needed to minimize hold-up volumes while being able to support the valves and yet provide access for potential diaphragm change-outs. For this project, a valve design that used multiple stacked actuators offered a particular advantage in this regard.

Because the facility where the skids would be installed required multi-product capability, the design dictated process flow turn-downs well-beyond normal ranges. As can be seen in Table A, the flow rate ratios were in the range of 50:1.

This required a combination of an in-line reducer system in tandem with variable frequency drives. In addition, the pumps themselves had to be carefully selected to assure that they had the ability to deliver the required flows within the pump RPM range produced by the selection of the VFD, motors, and reducers. As noted previously, this high turn-down requirement also dictated the use of a back-pressure control loop.

Once a combination of pump drives and variable frequency drives had been selected, the panel arrangement and operational methodology came into play. For this project, it was decided that a combination of auxiliary panels, local instrument panels, and local control panels would provide the greatest flexibility from an operator's perspective, while still providing appropriate separations with respect to power and signal applications.

The Auxiliary Panels (APs) were dedicated to housing solenoids, Festo blocks, and buss equipment. They were modeled off of a plant-wide standard that had been selected for the entire project. The C&D skid vendor then had the responsibility for design and fabrication of the panels and for their mounting on the skid. The local instrument panels were dedicated exclusively to the housing of analytical instruments and their local displays. These instrument displays had a requirement to display all information in real time. Finally, the control panels were mounted remotely from the skids themselves and housed in NEMA 4 panels. For this particular project, there was a desire to also utilize plant standards for the specifications and to drive the graphic user interfaces. This is another area in which the ability to customize a large skid for the owner creates benefits. Due to use of a Delta V platform, the C&D vendor wrote and provided the code, which was then loaded and run from the PWCS.

Even after the pumps and control systems have been properly specified and designed, it is necessary to bring a plant-wide view to the skids. Relative locations of the chromatography skids within a facility can have a direct impact on their functionality. In most instances, the purification suites will be located at an elevation below the buffer or product tanks. This can be problematic. As an example, there have been instances where, due to the combination of buffer tank sizes and relative head pressures above the skids, operators have experienced pump flow rates of up to 1/3 of the pump capacity with the pumps off! Proper piping design to allow throttling can resolve this issue.

In addition, the chromatography C&D skid vendor must receive direction on the inlet and outlet elevations for the skids prior to design. Having to lift product out of a trap in a suite, due to a low-level skid discharge point, can be a very expensive fix. However, with proper design and air blow-downs, it should be possible to keep losses between suites to well below 1%.

One more factor comes into play due to discharge elevation requirements imposed on the skid. This is the pump support system. Often the final skid product discharge height drives the pumps to a higher elevation, requiring them to be mounted mid-level on the skid. This can be seen in the photographs designated as Figures 2 and 3, where the pump height was set by the discharge elevation of the lowest outlet on the header, which in turn was a function of piping locations within the suite. When the pumps are elevated, one must be careful to introduce both enough structural strength in the skid itself for shipping, and enough mass to damp out vibration. Noise also may appear to be elevated from the operator's perspective, as the pumps approach ear-height. These problems are real, but manageable.

Fabrication and Testing

Because multiple skids were being constructed, DPS was able to use a phased approach for fabrication. This had several advantages. First among these was the ability to perform in-process inspections. These inspections allowed for changes on more than one occasion that created better value in the end product. Once an initial design was proven out, the other three units could be built in sequence. Because these were custom units, specific fabrication teams were selected to perform the same functions on each unit. This assured that delivery timelines were met, as there was no additional learning curve on each unit. Factory Acceptance Testing (FAT) was performed on the first unit 16 weeks after the project was begun by DPS with one skid completed every subsequent two weeks.

The FAT included complete dry and wet testing of the first unit, along with some loop tuning. All of the control modules were proven out, as were all of the instrument loops. Through judicious selection and standardization of the control modules and equipment modules early in the project, FAT was greatly reduced. This was done in a way that still assured compliance with GAMP. After FAT of the first skid, subsequent units were tested both wet and dry. However, the wet tests were limited to demonstrating pump curve compliance and functionality of all instruments that required flooded or flowing conditions. Final loop tuning on the three later units was able to be performed at the project site, based on the actual final conditions. Because this was an eventual commissioning requirement in any case, the time savings were significant. Figure 4 shows the 2-meter column with the C&D skid at its final location.

As is true in most projects, this one had its one major headache. This upset was in one of the simplest and most unexpected areas. Upon completion of all testing, when the drainability of the skids was being tested, the first skid failed. It was discovered that a machining error on the internal of the valves, visible only upon disassembly, had created an improper slope for horizontal configurations. This defect was impossible to detect during a typical incoming receipt inspection. The repair was fairly substantial, but the valve vendor accepted full responsibility to the extent of performing repairs during a normal factory shutdown period. The impact to the owner was minimal as repairs were able to be scheduled around the sequencing of the phased site testing of the skids. This turned out to be another welcome, albeit unexpected, benefit of the phased delivery of the skids.

Conclusion

Large-scale equipment has become state-of-the-art from the bioreactors through the purification suites in today's biopharmaceutical production plants. Many facilities have not yet focused on the bottlenecks in their plants to the point where they have been willing to up-scale their filtration and chromatography processes. Yet, those facilities that have increased their purification equipment throughput have found they are an easily incorporated element of the process. In addition, the larger units allow for more customization and better integration into the overall plant philosophy of control. For this project, careful preparation of the User Requirement Specifications, coupled with a specialty skid fabricator, created a fully integrated set of large-scale chromatography skids. With attention to several of the key process design parameters, as well as critical equipment selection and design factors, the largest biopharmaceutical chromatography skids built to date have been successfully put into operation.

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Energy Saving Tips for Designing Air Handling Units (AHUs) in Cleanrooms

This article provides recommendations for designing Air Handling Units (AHU) that will improve system operation and performance.

by Xingyun Mao

Introduction

The constant volume modular Air Handling Unit (AHU) with duct-mounted reheat coils has been widely used in AHU system design of pharmaceutical projects to provide cleanrooms with tight air temperature and humidity control, proper air distribution, and room pressurization. ASHRAE, ISO 14644-1 "Classification of Air Cleanliness," and cGMPs provide current guidelines in cleanroom particulate control and room classification, AHU load calculation, CFM requirements, system and equipment design and selection in the pharmaceutical industry.

Figures 1 - 3 show three common configurations of air handling systems. Their common practice is to use two stages of filters to prefilter the mixed air from outside and return air, cool it in the unit, reheat to a certain temperature, deliver to the room and clean area.

In Figure 1, all air goes through the air handler. A bypass damper provides load control and energy savings.

Figure 2 shows a return air bypass configuration. Only part of the return air mixed with outside air goes through the air handler. A circulation fan provides the system with static pressure requirement.

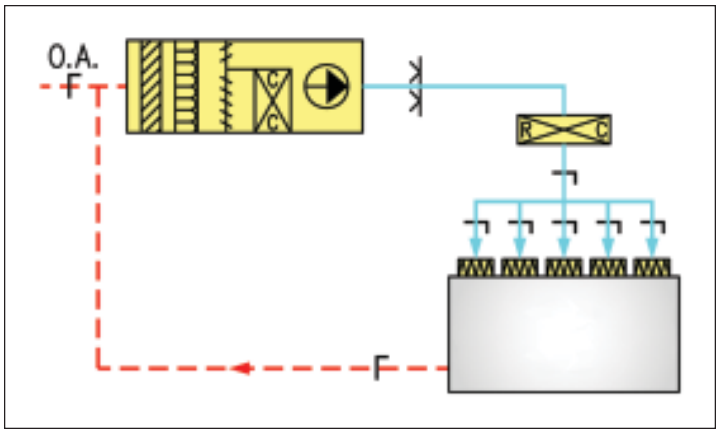

Figure 1. Air handling system with AHU bypass damper.

Figure 3 shows a Vertical Filter Module (VFM) structure. A VFM above the cleanroom works as a static box to provide pressure needs to room supply air. This configuration will greatly reduce the supply ductwork size, the disadvantage is multiple motors of circulation fans located in the air stream, which add up to cooling load.

Some AHUs also have exhaust and return fans for ventilation, keeping the system air balanced and the room pressurized.

Cleanroom AHUs in the pharmaceutical industry usually have a large amount of CFM and run 24/7, year around for contamination control, which dramatically increases energy cost and contributes to increased product pricing. The AHU selection and air treatment design could greatly affect system operation and performance, and contribute to system life time saving. The following tips offer energy savings in AHU system design.

Reduce the Use of Outside Air in Peak Load Seasons

In the hottest summer months, the outside air cooling load is usually two to three times that of the return air. Reducing the use of outside air and increasing the use of return air will dramatically reduce the cooling capacity required to overcome system cooling loads and meet indoor Cubic Feet per Minute (CFM) requirements. Reducing the use of outside air in the winter will reduce the heating load. The outside air must meet room pressurization, system leakage, equipment ventilation, and ASHRAE minimum ventilation requirements.

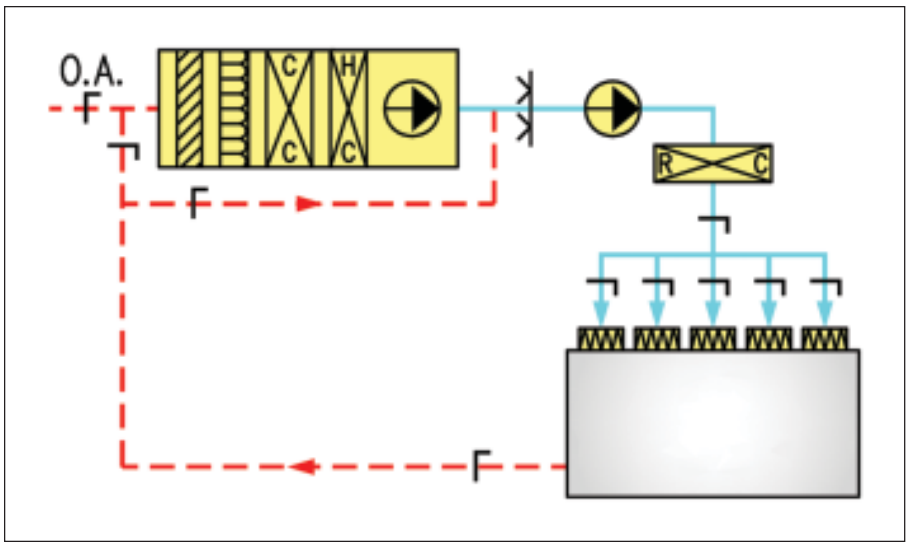

Figure 2. Air handling system with bypass return duct and circulation fan.

Increase the Use of Outside Air in Mild Weather Seasons

When the room requires cooling and the outside air enthalpy is lower than the return air enthalpy as it is in mild weather, it is good to increase outside air volume. Air enthalpy sensors and motorized dampers can provide outside air flow control. Increasing the outside air usage will increase filters' dust loading and shorten filters' life. There is a trade off between increase of outside air volume and filters' lifetime. The control is based on the wet bulb temperature or enthalpy difference between indoor and outdoor air, combined with outside air quality analysis.

Use Return Air to Premix with Supply Air to Provide Proper Supply Air Temperature

In hot weather, the mixed air is pre-cooled and then reheated to a certain temperature to provide the room with the proper supply air temperature and humidity control. Using return air to mix with the pre-cooled supply air instead of using the reheat coil reduces both cooling and reheat requirements. In some cases, this mixing may not reach required room supply air temperature, but at least it can reduce the reheat capacity requirement and improve the energy usage. The unit coil bypass damper configuration shown in Figure 1, the bypass return duct in Figure 2, and the multiple returns directly connected to the VFM in Figure 3 are three different methods to implement this function.

Increase Supply Air and Room Temperature Difference

In engineering design, a 5 to 13ºF temperature difference between the supply and the room air is usually acceptable. This temperature difference along with supply CFM and air distribution will decide indoor air temperature control accuracy, and is closely related with process, product, and human comfort. Increasing the temperature difference will reduce the room CFM required, as well as the size of the AHU and supply fan. The variation in temperature should be suitable for cleanroom particulate control or air changes, indoor temperature requirements in the working area, and human comfort.

Use Different Temperature Settings in Summer and Winter While Meeting Process Requirements

Some processes may allow the room to have different temperature settings in summer than in winter. Obviously, using a higher room temperature in summer and a lower temperature in winter will save energy. The choice to use different temperature settings in different seasons should be made after consulting with the equipment manufacturer and the process engineer.

Use an Economizer for Make Up Air

An economizer is a good choice for cleanrooms that have a large amount of ventilation and make up air requirements. An economizer uses exhaust to pre-cool outside air in summer and pre-heat it in winter. Although adding economizer will increase head loss to the system and the supply/return fan's pressure requirement, it will improve air energy utilization and could save operation costs. Before deciding to use an economizer, an economic analysis should be done for the life of the system.

Reduce System Control Accuracy

Most pharmaceutical processes require cleanrooms to be controlled at 60 to 68ºF and 30 to 60%RH. The design usually tightens to 65+/-2ºF and 45+/-5%RH. Reducing control accuracy will reduce start/stop frequency of cooling and heating equipment, save system operation costs, and potentially initial instrument cost.

Use a Variable Frequency Drive (VFD) to Control Supply Fan RPM

In an AHU system, there are three types of air filters, namely pre-filter, medium, terminal filter or TFM, each with a different lifecycle. The pre-filter and medium filter are used to pre-filter the mixed air and protect the final TFM. The supply or circulation fan should be sized for the filter's final pressure loss to compensate for the system/filter's lifetime. The pressure difference between filter's initials and finals can go up to 1/3 of the system's total loss. During the lifetime of the system, the supply fan runs mostly under design point. The changing supply air volume to cleanrooms could cause room pressurization malfunction. The re-sanitization of process facility and cleanroom are costly and time consuming. The AHU system design should consider system balancing, adjustment, and flow control. There are a few ways

to implement system adjustment, like changing fan blade pitch or replacing the belt and pulley. A VFD and a static pressure sensor on supply duct can provide better air flow control, reduce system routing balancing, and save energy cost average more than 10% annually.

Choose an AHU with Good Insulation and Low Air Leakage

AHUs with good insulation and low air leakage will reduce heat loss and save energy. Increasing unit insulation thickness will increase the initial cost, but could have lifetime savings.

Use the AHU as Your Make-Up Air Unit

Using an AHU to treat make up air instead of system air will greatly reduce unit size. Figure 1 is usually for a system with small amounts of CFM. In Figure 2, a part of the return air is mixed with outside air and pre-cooled, then mixed with another part of return air and supplied to the room to meet the room cooling load and supply air temperature requirements, as well as room CFM requirements. Both configurations shown in Figure 2 and Figure 3 are better choices regarding utilization of unit capacity.

Use Reheat Coils

Most AHU system designs use reheat coils to pre-heat supply air to meet room supply air temperature requirements and provide tight temperature control to individual rooms. Using a common reheat coil in an AHU for different rooms will reduce the size of end reheat coils, provide better energy control, and increase humidity absorption capacity of the supply air. The sizing and control setting of common reheat coil in an AHU unit should take into consideration each individual room's supply of CFM, cooling load, and control accuracy requirements.

Utilize Natural Resource and Low Value Energy

When possible, take advantage of natural resources such as well water to pre-cool the make up air and use hot water

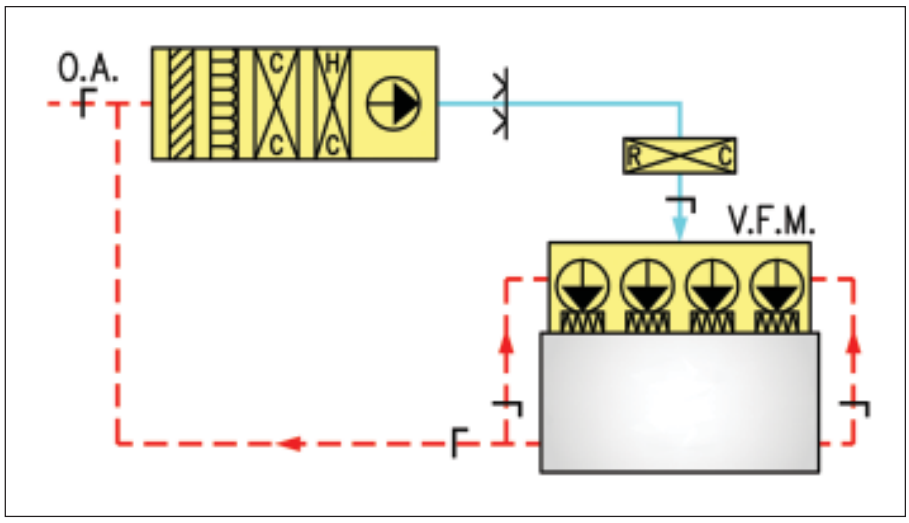

Figure 3. Air handling system with VFM configuration.

to reheat the supply air instead of using steam or electricity where there is a choice. Both will improve energy utilization.

Reduce Area with Higher Classification

Some cleanrooms, like fill rooms, require a Class 100 area surrounded by a Class 10,000 area. Higher cleanliness classifications require more air changes and CFM. Isolating the laminar flow to only the path of the product and using barrier to reduce the area of higher classification will dramatically reduce system CFM. Some test reports and articles also suggest reducing air changes while maintaining cleanroom laminar flow and particle control.

Raise the Air Temperature Leaving Cooling Coil

The selection of the air temperature leaving the cooling coil depends on the outside and indoor air temperatures, mixing ratio, indoor latent heat, and air treatment procedures. Increasing this temperature also will increase the chiller's evaporating temperature. Statistically, raising the chiller's evaporating temperature by 1°F will increase its output average by 2 to 4%. Raising the evaporating temperature also will improve the chiller's efficiency.

Choose Correct Safety Factors

The safety factor may not affect system energy consumption significantly, but it will improve system efficiency. When picking up outside and indoor air design parameters, calculating the cooling/heating load, room and system CFM, and selecting a coil, each stage could have a safety factor involved. The increased number of safety factors

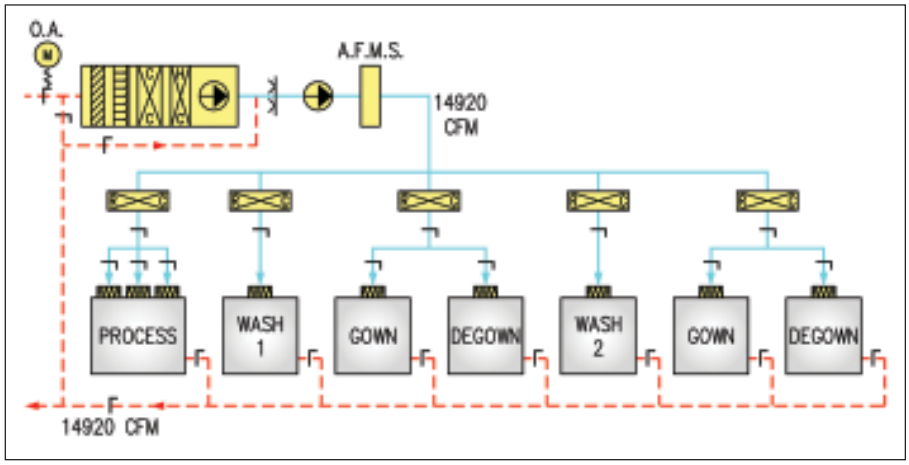

Figure 4. Air handling system for a specific project.

Filter	Initial "wg	Final "wg	Life Time
30% THROWAWAY 2"	0.18	0.5	3-6 months
65% CARTRIDGE 12"	0.39	1.2	1-2 years
TFM	1	2	5-10 years

Table A. Air filter resistance and expected life.

could cause the system to be oversized by 30 to 50% and lead to low system efficiency, increase the system's initial cost, and possibly increase heat loss. Common practice is to design the unit and system with a 10 to 20% safety factor.

The specifications discussed above may not be suitable for all projects; however, a thorough study and understanding of user requirements can result in an AHU design that improves system operation and performance; resulting in reduced costs. The following engineering design examples illustrate how to maximize system bypass CFM to minimize AHU size and to use VFD to compensate for three-stage filters' lifetime head loss.

User requirement: to design a clean air conditioning system for part of a process and related area, totaling seven rooms. The process requires the room temperature to be kept between 60 and 66°F, relative humidity 35 to 65%, year around. The outside air design parameter: summer 93° Fahrenheit dry Bulb (FdB)/75° Fahrenheit wet Bulb (FwB), winter -11°F. A centralized chiller station provides 35°F chilled water.

After a physical study, an AHU system similar to Figure 2 was selected with five reheat zones. The system is shown in *Figure 4*. Table A includes three stage air filters' initial and final resistance, along with their expected lifetimes. In this practical example, the room latent heat is considered trivial.

For simplicity and illustration, the redrawn air system is shown in *Figure 5*. Seven cleanrooms are combined as a use point. Using room supply air, return air, and system leakage, the AHU make up air volume is calculated. Based on the estimated AHU CFM and preliminary ductwork layout, the AHU supply fan 15hp and system circulation fan 20hp are selected. The ASHRAE Handbook specifies the heat gain from the blower with respect to motor location relative to the air stream. The air temperature increase across each blower is calculated. Considering the ductwork heat loss and air leaving cooling coil temperature and using heat equilibrium of air at node A, the minimum AHU CFM is calculated. The results are shown in *Figure 5*. If without the bypass, the unit would need to treat all the supply air. The unit would be two to three sizes larger. This would require more space and increase architectural cost.

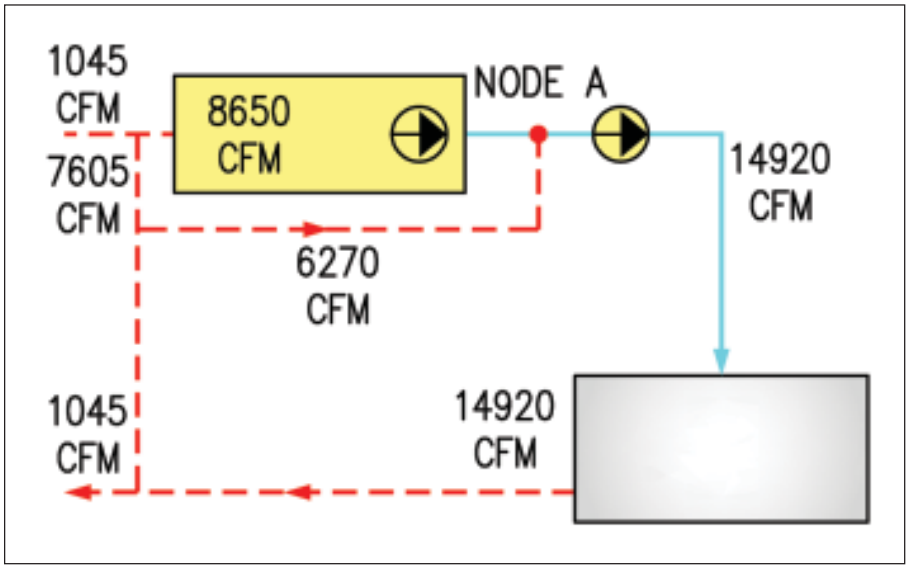

Figure 5. A simplified sketch.

Table B shows the temperature increase at each component and design point used in the calculation.

In this configuration, a part of return air premixed with outside air, cooled, and then mixed with bypass air, goes through the circulation fan to heat up to the room supply air temperature. Under these design conditions, the reheat coils will not need to work.

The flexibility of the system allows us to use the temperature difference between the air leaving the coil and the room supply air to size the reheat coil in the unit, and use the room supply and return air to size the zone coils. Engineers can select the coil based on their specific situations and needs.

As we mentioned earlier, the system flow control provides cleanrooms with proper air distributions and pressurizations. Due to the operation characteristics of the filters, the pressure difference between filters' initials and finals could reach to 1/3 of the system total head loss.

Figure 6 shows the filters' resistance increases vs. their average lifetime based on the data listed in Table A, assuming that a filter dust loading and resistance are gradually increased. A drop on the curve means there is a filter replacement during that period.

Table C is a set of operation data which shows the pressure loss of each component and pressure of supply fan's for a typical system based on an engineering test and balance report. In this example, there is no circulation fan.

From Table C, the system initial pressure loss is 4.71"wg. To properly size the supply fan, its head should cover system (filters) final loss. In this case, the system initial pressure loss is about 69% of the finals. For the most time, the supply fan will run at its 69 to 100% of equipped capacity. According to fan's laws, a fan's pressure is proportional to its revolution squared. The system static pressure change will account for 17% of fan's rpm adjustment. In order to provide the system with

Cooling Coil T	Supply Fan ΔT	Circulation Fan ΔT	Room T	Supply Duct ΔT	Return Duct ΔT
42	4.75	3.16	60 - 66	1	1

Table B. Air temperature calculation for a practical example (°F).

AHU CFM	Filter Pre&Med Filter	Cooling Coil	Heating Coil	Fan		Motor HP
				Ext	Total	
10650	0.57	0.98	0.12	3.04	4.71	25

Table C. System head loss from a typical test and balance report ("wg).

constant CFM and room pressurization, a proper pressure monitoring and flow control system should be considered.

A motor Variable Frequency Drive (VFD) and static pressure monitoring system can provide air system dynamic flow control to meet room pressurization needs and save energy. To illustrate, we use motor hp, system static pressure in Table C, filter initial and final pressure drops in Table A, and assume VFD has 97% efficiency (for engineering purposes), system running 330 days a year, electricity unit price $0.08/kwhr. We calculate that a VFD can save an average of 13% of fan's power consumption or $1,532 a year during the system's lifetime. The VFD's initial cost could be recovered by a system in the first couple of years with these savings.

There are some other common practices which also can contribute to the reduction of cleanroom cooling/heating load requirements, AHU system heat loss, and improve system efficiency, such as the increase of architectural and ductwork insulation, isolation of heat-generating equipment, replacement of filters regularly, choice of dampers and duct-mounted reheat coils with low air leakage, improvement of construction quality, selection of proper heating/cooling system and controls. A good manufacturer's maintenance practice or protocol also contributes to the system's energy savings. Reducing architectural air leakage includes increasing wall and ceiling seamlessness, selecting doors and windows with good seals, reducing the number of wall penetrations, using pressurized pass-thrus, and properly sealing and blocking openings and penetrations. Leadership in Energy and Environmental Design (LEED) provides guidelines in building energy utilization and indoor air quality, among others. Poor ductwork and system construction could contribute up to 15% or more of system CFM increase and greatly increase system makeup air volume. An AHU system lifetime economic analysis should be conducted before insulation thickness is selected.

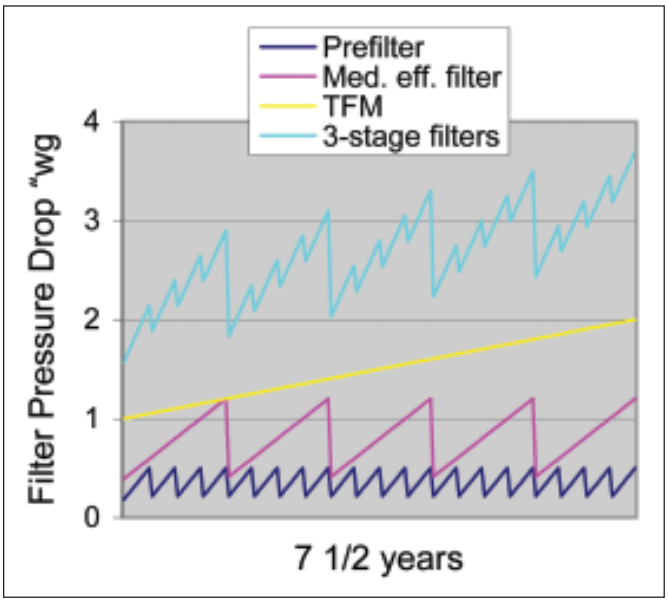

Figure 6. Filter resistance vs. lifetime.

A good design is a combination of system planning, equipment selection, sizing, and placement. It also needs to consider system adaptation and expansion for future use, construction requirements, and maintenance. Cutbacks on the initial investment of the units and the system could limit its capacity and cost more to operate.

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Equipment Cleaning Validation Modeling Approach for Clinical Trial Compounds

by Lisa Ray, Dr. Brian Pack, Dr. Lisa Wenzler, and Travis Coy

This article outlines the theory and implementation of the equipment cleaning validation strategy in Clinical Trial Packaging at Eli Lilly and Company using model compounds, and describes the process for managing the equipment cleaning validation program.

Introduction

The objective of an equipment cleaning program is to establish documented evidence that the cleaning process consistently provides a high degree of assurance that production equipment is free from materials that could contaminate subsequent products. A cleaning verification program or a cleaning validation program provides this documented evidence. Cleaning verification consists of routine monitoring of equipment cleaning processes. Routine monitoring is accomplished by a variety of techniques including: visual inspection,[1,2] swab analysis,[3] and rinse-solution analysis.[4] Cleaning validation confirms the effectiveness of a cleaning procedure and eliminates the need for routine testing. Validation is defined by the Food and Drug Administration (FDA) as a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.[5] As stated in Annex 15 to the EU Guide to Good Manufacturing Practices, cleaning validation can be performed as a prospective validation for a specific product or it also is considered acceptable to select a representative range of similar products and processes.[6] This representative range of similar products and processes are commonly termed "model compounds."

Model compounds can be chosen on the basis of solubility, structure, potency, and/or compounds that otherwise pose a unique challenge to the cleaning process. After selection of the model compounds, an experimental approach for validation may be performed by spiking equipment with a known amount of product, cleaning the equipment, and collecting data from direct surface sampling (i.e., swabbing). If enough data is gathered and deemed acceptable, a cleaning validation package may be assembled and routine swabbing is no longer required for products represented by the model compounds. The cleaning validation data are considered acceptable if the established cleaning acceptance limits are satisfied on each surface. The focus of this article is to outline the theory and implementation of the equipment cleaning validation strategy in Clinical Trial Packaging using model compounds. In addition, the process for managing the equipment cleaning validation program in Clinical Trial Packaging is described.

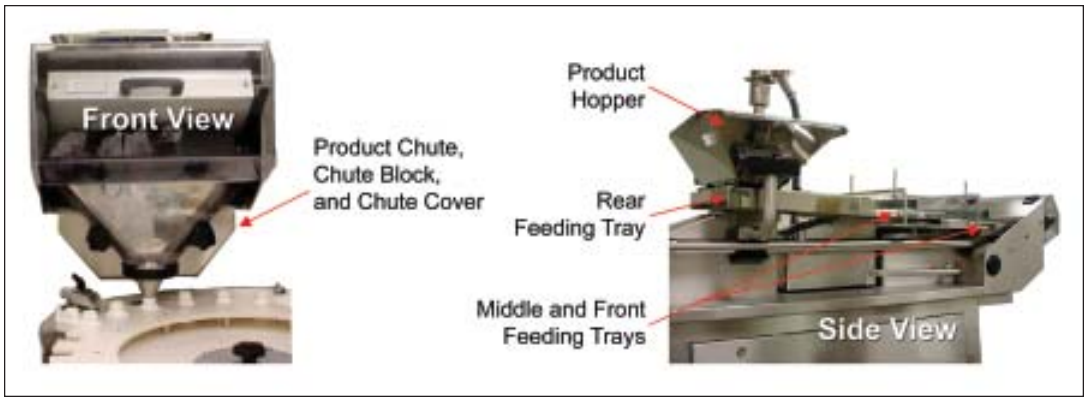

Figure 1. Bottle filler 1.

Figure 2. Blister machine 1.

Model Compounds

Cleaning validation is typically executed by demonstrating that the cleaning process utilized on multiple lots of the same material and process is adequate to reduce the level of active pharmaceutical ingredient below a certain safety limit. Due to the nature of clinical trial materials, such as unpredictable lot sizes or modifications to the formulated drug product, three identical lots of a product/formulation manufactured by the same process may not be packaged until a later stage of development when the process has been locked and the size of the clinical trials has increased. In addition, it is not uncommon for a clinical trial packaging department to support 20 to 30 compounds at any given time. Therefore, performing cleaning validation on a single compound may not be feasible. As previously described, it also is considered acceptable to select a representative range of similar products and processes and perform a model-compound cleaning validation.

Table A contains information associated with the five model compounds chosen for execution of equipment cleaning validation in Clinical Trial Packaging. All five model compounds are solid oral dosage forms (i.e., tablets or capsules). Many parameters were considered during the selection process for these compounds. The structure of the compound, pKa (negative log of the acid ionization constant), functional groups, solubility, and dose/potency of the compound were all key considerations in the selection process. Since pKa and functional substitutions play a key role in determining solubility, solubility was selected as the key parameter used to define the model compounds based upon its ability to influence the cleaning effectiveness of a particular agent. In combination with the dose/potency of the compound, a large number of compounds can ultimately be represented by this model. Table A provides solubility information (in water, 0.1 N HCl, 0.1 N NaOH, and methanol) for the model compounds in addition to the lowest and highest strength manufactured. The solvents used for the solubility screen were chosen for a variety of reasons. First of all, an aqueous cleaning agent is typically utilized in the Clinical Trial Packaging area. Acidic or basic cleaning agents also can be utilized when aqueous solubility is not sufficient. For difficult to clean compounds, it is common practice to utilize a methanol wipe to provide added assurance that no residue is present. Finally, the solubility in these selected solvents is readily available from the analytical chemist in preparation for the first regulatory filing.

The model compounds have differences in solubility that represent all compounds currently packaged in the Clinical Trial Packaging area. Compound A and Compound C are practically insoluble in water, HCl, and NaOH and slightly soluble in methanol. Compound B is sparingly soluble in water and HCl, practically insoluble in NaOH, and freely soluble in methanol. Compound D is practically insoluble in water, HCl, NaOH, and methanol. Compound E is soluble in water, practically insoluble in HCl, and freely soluble in NaOH and methanol. In addition to differences in solubility, the model compounds represent a wide range of manufactured strengths in either a tablet or capsule formulation (i.e., 0.5 mg to 50 mg for the smallest strength manufactured and 0.75 mg to 200 mg for the highest strength manufactured) and a variety of chemical structures. The lowest strength manufactured is included in Table A since the acceptance

Compound Name	Solubility	Lowest Strength Manufactured	Highest Strength Manufactured
Compound A	Practically insoluble[1] in Water, HCl, and NaOH Slightly soluble[2] in Methanol	25 mg	200 mg
Compound B	Sparingly soluble[3] in Water and HCl Practically insoluble in NaOH Freely soluble[4] in Methanol	2.5 mg	100 mg
Compound C	Practically insoluble in Water, HCl, and NaOH Slightly soluble in Methanol	2.5 mg	20 mg
Compound D	Practically insoluble in Water, HCl, NaOH and Methanol	0.5 mg	0.75 mg
Compound E	Soluble[5] in Water Practically insoluble in HCl Freely soluble in NaOH and Methanol	50 mg	200 mg

[1]Practically insoluble = < 0.1mg/mL
[2]Slightly soluble = 1-10 mg/mL
[3]Sparingly soluble = 10-33 mg/mL
[4]Freely soluble = 100-1000 mg/mL
[5]Soluble = 33-100 mg/mL
NOTE: Solubility definitions consistent with USP.

Table A. Model compounds.

limits for cleaning verification (i.e., swabbing) for compounds are determined using the lowest dosage strength according to local procedures; the model compounds also represent a range of cleaning acceptance limits. The highest strength manufactured is included in Table A to portray the wide range in manufactured strengths represented by the model compounds. Compound A is a colored powder in a tablet formulation that poses the potential for staining or smearing equipment contact surfaces during the manufacture and/or cleaning process itself. Therefore, Compound A was included as a model compound based on solubility and its unique cleaning challenge.

Model Compound Cleaning Validation Strategy for Clinical Trial Packaging

A model compound equipment cleaning validation protocol was written to generate cleaning verification data via direct surface sampling (i.e., swabbing) following the established standard cleaning procedure in Clinical Trial Packaging. The purpose of generating this swab data was to validate that the cleaning agent successfully cleans all model compounds from the Clinical Trial Packaging equipment. The cleaning agent utilized is a non-caustic (pH 9) cleaner containing an emulsifier, dispersing agent, corrosion inhibitor, and two surfactants and historically has been a very effective cleaning agent. Utilizing one cleaning agent in the Clinical Trial Packaging area can simplify the cleaning procedures and ultimately improve efficiency. Fourteen separate product contact locations across four major pieces of equipment utilized in Clinical Trial Packaging were selected for execution of this protocol. The selected swab locations shown in Table B represent the material of construction of all product contact surfaces in the Clinical Trial Packaging area (i.e., 316 stainless steel, acetal, polycarbonate, and glass).

The equipment chosen represents all Clinical Trial primary packaging operations that includes both bottle filling and blister packaging. This validation incorporated swabbing an automated bottle line (BF1 in Table B), two blister machines, and a semi-automatic bottle filler (BF2 in Table B). All of which are used routinely in Clinical Trial Packaging. A variety of equipment sizes, shapes, surfaces, and functions are included in this list of machinery. The automated bottle line shown in Figure 1 represents a large bottle filling operation.

The blister machine shown in Figure 2 represents a large blistering machine (Blister Machine 1 in Table B). The blister machine shown in Figure 3 represents a small blister filling machine (Blister Machine 2 in Table B). The semi-automatic bottle filler shown in Figure 4 represents a small bottle filling machine.

The surface area per component is listed in Table B since surface area is one of the four factors that determine the number of swabs per component. If a component's surface area represents 25% to 75% of the total surface area of the equipment, one swab is dedicated to the component. If a component's surface area represents more than 75% of the equipment's total surface area, two swabs are dedicated to

Figure 3. Blister machine 2.

that component. There are three other factors that contribute to the total number of swabs: energy dissipation, material of construction, and cleaning difficulty. A detailed description of the justification process for the number of swab locations and calculations to establish acceptance limits can be found in a previous article.[7]

Rather than performing cleaning operations following a packaging run for a model compound, it was decided to soil the product contact surfaces for execution of this protocol. Surfaces were prepared by soiling the equipment (at the designated swabbing location) with the contents of three dosage units of the highest strength of each model compound. The highest strength of each model compound is shown in Table A. By nature of contacting mainly intact dosage forms in Clinical Trial Packaging, equipment is routinely not heavily soiled. Therefore, exposure of all product contact locations with the milled contents of three capsules or three milled tablets represents a worst-case scenario of potential product contact. Prior to cleaning, the equipment was held dirty for three days prior to cleaning to represent a three-day dirty hold time.

Clinical Trial Packaging personnel manually cleaned the equipment for two minutes using diluted cleaning agent prepared in purified water (65° C). Following the manual clean, equipment was rinsed for one minute with purified water (65 ° C). Once the equipment was completely dry and visually clean, each swab location was sampled by swabbing a 16 inch^2 location. The swabbing procedure dictates that 20 strokes are executed in the horizontal direction, the swab is flipped, and then 20 vertical strokes are performed. Swabs used for this investigation were Texwipe Alpha™ large. Each swab was then immersed in 5mL of an appropriate sample solvent in order to extract the analyte. An aliquot was then taken for analysis. All swabs were analyzed with validated methods employing either UV spectrometry or High Performance Liquid Chromatography (HPLC) with UV or fluorescence detection and compared versus a standard prepared at an appropriate concentration (i.e., near the acceptance limit). The recovery of the active pharmaceutical ingredient from

Component	Material of Construction	Surface Area (sq. inches)	# Swabs
Product Hopper – Bottle Filler 1 (BF1)	316 Stainless Steel	603	1
Product Feeding Tray (BF1)	316 Stainless Steel	735.8	1
Chute Block (BF1)	Acetal® (chemical name representative for Oilon®)	170.2	1
Chute Cover (BF1)	Polycarbonate (chemical name representative for Vivak®)	136.2	1
Product Chute (BF1)	316 Stainless Steel	29.7	1
Product Hopper – Bottle Filler 2 (BF2)	316 Stainless Steel	380.3	1
Product Feeding Tray (BF2)	316 Stainless Steel	82.1	1
Turntable Disc (BF2)	Glass	263.9	1
Turntable Disc (BF2)	316 Stainless Steel	263.9	1
Product Chute (BF2)	Polycarbonate (chemical name representative for Lexan®)	10.8	1
Product Filling Tray – Blister Machine 1	316 Stainless Steel	1326.9	3
Product Filling Tray – Blister Machine 2	316 Stainless Steel	442.3	1

Table B. Equipment product contact and swab locations.

each surface material had been determined during method validation and was corrected for in these assays.

Acceptance limits were calculated based on the smallest manufactured dosage strength for the model compounds. The acceptance limits shown in Table C that were utilized for execution of Model Compound Cleaning Validation in Clinical Trial Packaging are the acceptance limits that are used in the cleaning verification program.

All swab results from all swab locations generated per this protocol were reported as pass when compared to the acceptance limit. There were two polycarbonate surfaces (Bottle Line chute cover and Semi-Automatic Bottle Filler chute) that were not visually clean following Compound A spiking, cleaning with cleaning agent for two minutes, and rinsing for one minute. The protocol instructions (and local cleaning procedures) indicated that the surface must be visually clean prior to swabbing. Therefore, a methanol wipe was added for these two surfaces to obtain a visually clean surface. Since a methanol wipe was required to obtain a visually clean surface for two polycarbonate surfaces after spiking with Compound A, a methanol wipe was incorporated as the final cleaning step in the validated cleaning procedure. The implemented validated cleaning process is a two minute manual clean using cleaning agent, followed by a one minute rinse with purified water, followed by a methanol wipe and a visual inspection. Even though the methanol wipe was not required to achieve a visually clean surface for all other swab locations and surfaces, the methanol wipe was added for all compounds to account for future compounds that are practically insoluble in water, and may or may not leave a visible residue. Remember that compound A is colored, but most compounds are practically white and may be difficult to detect on a white polycarbonate surface. The addition of a methanol wipe, which is neither a work nor a time intensive process, provides a consistent, conservative method of cleaning for all compounds. If equipment is not visually clean following execution of the cleaning process that includes the methanol wipe, the cleaning process will be repeated until visually clean surfaces are obtained.

Since the visual inspection was implemented to replace routine swabbing, a definition and example of visually clean was provided to the Clinical Trial Packaging area. Figure 5 provides a cleaning pictorial for a product filling tray utilized on Blister Machine 1 and also contains cleaning instructions, which are outlined in a local procedure, and the visual clean definition and example. The main purpose of the pictorial is to provide operators an example of a visually clean filling tray on Blister Machine 1.

Lastly, the cleaning process is only considered validated when equipment is cleaned within three days of completion of use. The decision for validation of a three day dirty hold time was driven by the Clinical Trial Packaging area. These three days represent equipment that sits dirty over a weekend. For example, if a blistering run was completed late on a Friday, the "dirty" filling tray associated with that blistering operation may sit over the weekend prior to cleaning. Validation of a three day dirty hold time allows for equipment to sit for three days after use prior to cleaning.

Clinical Trial Packaging Model Compound Spreadsheet

After protocol execution and before implementation of the

Figure 4. Bottle filler 2.

cleaning validation strategy in Clinical Trial Packaging, a Clinical Trial Packaging Model Compound Spreadsheet was generated to provide detailed correlations of all compounds packaged in the Clinical Trial Packaging area to the model compounds based on their solubility. The actual spreadsheet lists all five model compounds followed by all products that are currently packaged in the Clinical Trial Packaging area. An example of this spreadsheet is shown in Table D.

The actual spreadsheet contains the compound name, compound number, structure, solubility information (in water, 0.1 N HCl, 0.1 N NaOH, and methanol), lowest strength/dosage form, number of historical swabs, and a rationale/comparison to the model compounds. The purpose of this spreadsheet was to document that the model compounds are representative and inclusive by providing detailed correlations of all compounds currently packaged in the Clinical Trial Packaging area to the model compounds. A total of 725 historical swab results (reported as pass or fail) were compiled in the Clinical Trial Packaging area since 2003. All historical swab data were generated after manually cleaning with cleaning agent. Out of the 725 swab results, there were only 11 swab failures (swabs passed 98.5% of the time). All swab failures associated with the cleaning verification program have been addressed with implementation of disposable equipment (i.e., hand paddles and product tubes) and are associated with compounds that are soluble in methanol, but insoluble in water (i.e., Compound A). Therefore, methanol wipes address the remaining 1.5% of cleaning failures where cleaning agent alone was not sufficient. Thus, there is a high degree of confidence in the validated cleaning procedure that incorporates a methanol wipe to effectively clean the equipment below the cleaning limit.

Compound	Small Manufactured Dose (mg)	Acceptance Limit (µg/swab)
Compound A	25	5.0
Compound B	2.5	5.0
Compound C	2.5	5.0
Compound D	0.5	0.5
Compound E	50	5.0

Table C. Acceptance limits for model compounds.

Summary

Per execution of the Model-Compound Cleaning Validation study in the Clinical Trial Packaging area, a two minute manual clean using cleaning agent, followed by a one minute rinse with purified water, and a methanol wipe was validated. Even though the methanol wipe was only needed to obtain a visually clean surface for two polycarbonate surfaces following spiking with Compound A, it was added for all compounds from this point on to account for future compounds that are practically insoluble in water. This procedure also will provide a consistent, conservative method of cleaning for all compounds. Furthermore, routine visual inspections will replace swabbing for equipment in Clinical Trial Packaging. The locations selected for visual inspection are the previous swab locations justified using the process described in a previous article.[7] The visual inspection locations have been communicated to Clinical Trial Packaging personnel through equipment cleaning instructions implemented for each piece of product contact equipment in Clinical Trial Packaging.

The validated cleaning process implemented in the Clinical Trial Packaging area directly contributes to the development of new medicines by eliminating workload associated

Compound Name	Solubility	Lowest Strength Manufactured	Historical Swabs	Rationale
MODEL COMPOUNDS				
Compound A	Practically insoluble in Water, HCl, and NaOH Slightly soluble in Methanol	25 mg	68	Model Compounds chosen based on solubility
Compound B	Sparingly soluble in Water and HCl Practically insoluble in NaOH Freely soluble in Methanol	2.5 mg	99	
Compound C	Practically insoluble in Water, HCl, and NaOH Slightly soluble in Methanol	2.5 mg	70	
Compound D	Practically insoluble in Water, HCl, NaOH and Methanol	0.5 mg	49	
Compound E	Soluble in Water Practically insoluble in HCl Freely soluble in NaOH and Methanol	50 mg	55	
REMAINING COMPOUNDS				
Compound 1	Practically insoluble in Water Sparingly soluble in HCl Very slightly soluble in NaOH Slightly soluble in Methanol	1 mg	56	Solubility profile between Compound B and Compound A/ Compound C
Compound 2	Freely Soluble in Water and HCl Slightly soluble in NaOH Sparingly soluble in Methanol	5 mg	8	Solubility profile between Compound E and Compound B

Table D. Clinical trial packaging model compound spreadsheet.

Figure 5. Cleaning pictorial for product contact parts on blister machine 1.

with analysis of routine Clinical Trial Packaging swabs. This benefit is realized in both the analytical laboratories and the Clinical Trial Packaging area through elimination of approximately 500 swab analyses per year. Since packaging equipment is now available for use immediately following equipment cleaning and a visual inspection, the one to five day equipment downtime awaiting swab results is also eliminated. This efficiency equates to greater equipment utilization and decreased packaging cycle time.

To ensure on-going correlation of new compounds to the model compounds, a database was created listing all oral products currently packaged in the Clinical Trial Packaging area in addition to new compounds that will be packaged in the near future. The database provides the compound name, compound number, structure, solubility information (in water, 0.1 N HCl, 0.1 N NaOH, and methanol), lowest strength/dosage form, and a rationale for comparison to the model compounds. Since this information is subject to change (i.e., addition of new compounds), this database and the cleaning program will be evaluated regularly.

Lastly, a solubility matrix has been developed using the solubility information in the Clinical Trial Packaging Model Compound Spreadsheet. The model compounds are listed at the top of the solubility matrix in order of increasing solubility. All other compounds currently packaged and new compounds, which will be packaged in the near future, have been placed on the solubility matrix according to each compound's specific solubility profile. The actual solubility matrix lists all five model compounds across the top followed by all products that are currently packaged in the Clinical Trial Packaging area. An example of this spreadsheet is shown in Table E.

The purpose of the solubility matrix is to provide a one-page summary that visually shows that all compounds currently packaged and planned for future packaging are represented according to solubility by the model compounds. The solubility matrix is used as a tool that is revised regularly (i.e., addition of new compounds) by the owner of the Clinical Trial equipment cleaning program. Compounds that require special consideration regarding equipment cleaning (e.g., cytotoxic compounds) will be given additional consideration

Practically Insoluble	Practically Insoluble/ Slightly Soluble		Sparingly Soluble/ Freely Soluble		Soluble/ Freely Soluble
Compound D	Compound A/ Compound C		Compound B		Compound E
Solubility Similar to Compound D	Solubility Similar to Compounds A and C	Solubility Between Compounds A, C, and B	Solubility Similar to Compound B	Solubility Between Compounds B and E	Solubility Similar to Compound E
Compound 3	Compound 4	Compound 1	Compound 6	Compound 2	Compound 8
		Compound 5		Compound 7	Compound 9

Table E. Solubility matrix.

prior to addition to the Clinical Trial Packaging Product Listing and/or solubility matrix.

Future Work

Execution of model compound cleaning validation also is planned for equipment utilized in the Clinical Trial Oral Manufacturing area that only contacts intact capsules or tablets. Examples of this type of equipment include final product weight sorters, capsule polishers, and/or metal detectors.

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Acknowledgments

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Aseptic Filling of Closed, Ready to Fill Containers

by Jacques Thilly, Doris Conrad, and Christian Vandecasserie

This article presents a closed vial filling technology. It details the vial and stopper design, manufacturing, the e-beam surface sterilization unit, the filling equipment and process, and sealing laser technology.

Introduction

The concept presented in the discussion below includes the following two elements: a plastic closed vial, gamma sterilized, and a new filling and capping process under Restricted Access Barrier System (RABS) located in a Class C room.

The Vial

The vial combines the following two key features:

- It is a ready to fill container, meaning that there is no washing or sterilization required in line with the filling process.
- It is closed by a secured stopper, resulting in three advantages:
  - No stopper washing, siliconization, or sterilization is needed at point of use (same advantage as ready to use stopper).
  - No stopper introduction, feeding, or placement in line with the filling process is required.
  - Closure integrity is provided at the start, and does not result from an adjustable crimping process, most of the time located in an adjacent Class C room.

The cap design provides a seal against the stopper surface and protects the aseptic piercing target of the stopper (caps are gamma sterilized and placed in line under the RABS).

The added advantage of protection of the inner sterility of the closed container is associ-

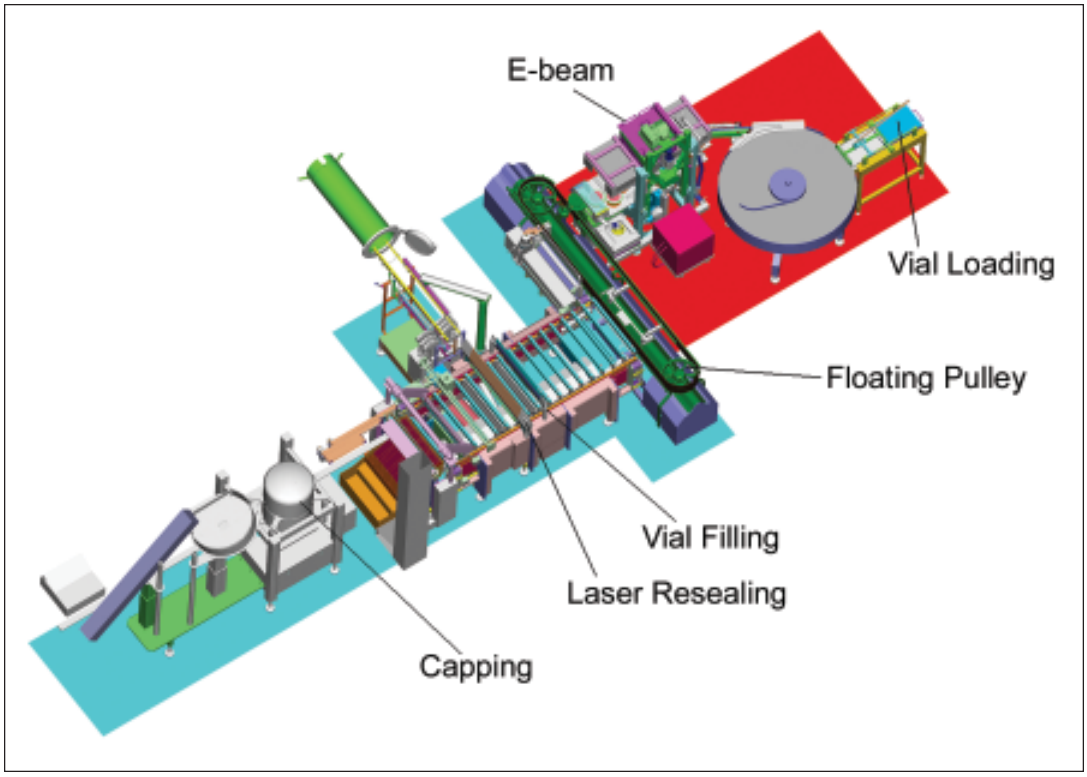

Figure 1. The closed vial filling line.

Figure 2. The closed vial before and after capping.

ated with the use of RABS instead of semi-closed isolators with VHP sterilization process. The active RABS is described as follows:

- Vertical integral laminar flow, providing Class 100A conditions with air escaping at the bottom and no overpressure
- Rigid walls, glove ports, and Rapid Transfer Ports (RTP)
- E-beam surface sterilization at the vial entrance

The Filling and Capping Processes

The filling and capping made up of five steps: see filling line layout in *Figure 1*:

1. A vial loading station under regular laminar flow
2. A truly "mini" e-beam to sterilize the vial top surface
3. An extremely strong, non-coring filling needle which pierces the stopper, fills the liquid product into the vial, and vents the overpressure
4. A highly calibrated laser immediately re-seals the needle puncture.
5. Plastic capping (simple snap fit assembly) takes place in line under the aseptic conditions in the barrier.

Below are more detailed descriptions of the above elements.

Vial Design

A range of vial sizes from 2mL to 100mL is defined: all sizes have a bottom ring (to securely hold the vial at its base when the filling needle is withdrawn from the stopper), and because all vial sizes have the same neck finish, only one size of stopper and cap is needed.

Two simple and solid non-return snap fits assemblies are used to secure the top ring onto the stopper and the plastic cap onto the top ring.

The healthcare provider will find the injection withdraw target on the stopper in an aseptic condition since it has been protected by the sealing rib under the removable sector of the cap.

The stoppered vial successfully passes a severe integrity test: dye penetration after three cycles of consecutive exposure during 30 minutes to vacuum (-300 mbars) and another 30 minutes to pressure (+150 mbars). The stopper skirt is bearing against the vial inner neck diameter and the stopper flange is compressed by a sealing rib. This rib is concentrating a strong pressure while general stress on the plastic remains at a low level. Polymer to polymer natural adherence develops over time between stopper and vial body, further enhancing a robust closure integrity.

Cyclo-Olefin Co-polymer (COC) is used for the highly transparent vial body. Its purity and excellent barrier properties are already well appreciated and well tested in plastic prefillable syringes.

The stopper is made of a special formulation of Thermo Plastic Elastomer (TPE) produced by a large international compounding company. Regular vulcanized elastomer formulations would not be suitable as they would burn (without remelting) under laser heat. The elastomeric TPE material is remelting exactly like any other thermoplastic material.

Both materials pass USP Class VI test requirements after gamma sterilization (tested at worst case 50 kGray). Also, both materials did not generate pH drift outside of Pharmocopeia limits when in contact with Water For Injection (WFI).

Vial Manufacturing

Two molding machines, which produce the vial body and the stopper, have their clamping unit in cantilever configuration in a room Class 100A (with full environment monitoring and validation). Both components are picked directly from their respective molds by cleanroom robots that only touch the components on non-critical surfaces for immediate assembly. Internal particles, bioburden, and endotoxin are extremely low and no chemical agent is used to assist the molding operation. Therefore, vial or stopper washing is not necessary. Gamma sterilization of the assembled and closed vial at minimum 25 kGray provides a high level sterility assurance.

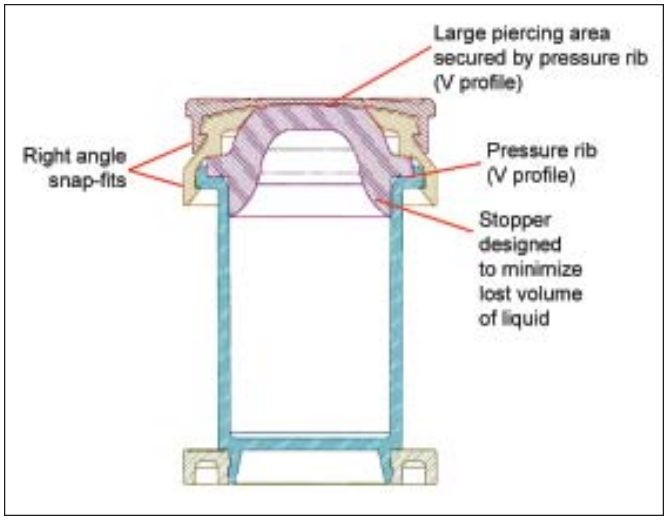

Figure 3. Cross-section view of the closed vial.

Mini E-Beam Surface Sterilization

Unloading of vials, under laminar flow, at the entrance of the filling line is designed to keep the operator's hands away from the vials. A new design of corrugated **Polypropylene** (PP) boxes is helping to achieve that goal. Nevertheless, recontamination may occur on the outer surfaces of the vial assembly and for that reason, the critical top surface of the vial (stopper and surrounding top ring surface) is re-sterilized by e-beam, just before entering the filling barrier.

E-beam is a very effective process for surface sterilization, at minimum 25 kGray, penetrating the material up to 30 microns (no "shadow" effect as found with processes using light). A stack of very thin (10 microns) film dosimeters is used to assess this. Vials are transported at constant high speed, in single row, under a mini e-beam generator (the power is 50 kilo-electron-Volts only) allowing for rather light lead protection (4 mm thick) shielding against X-rays. This protective shielding can be lifted (for accessing the conveyor) by a simple command signal from the operator's panel.

Daily checking of dose is achieved by running a special vial with a dosimeter (radiochromic film) through the e-beam unit. Speed and power are continuously recorded from separate sensors into a logger, similar to how a sterilizing tunnel is routinely controlled.

Beam configuration is composed by eight consecutive, static filaments in the same vacuum chamber. Each filament is individually controlled. The low power of the unit permits air cooling instead of water cooling which is a clear advantage.

Filling Needle

Robustness derives from its 13 gauge size (0.095" = 2.4 mm OD) with very thick walls (0.0157" = 0.4 mm). The tip is made of solid plain stainless steel with a pencil point shape. The liquid product flows downward through two lateral openings at a 30° angle from the vertical. This ensures a gentle flow of up to 10 cc/second without splashing against vial walls. The needle is non-coring (no visible particles as the pencil point penetration is not achieved by sharp edges likely to cut into the stopper and holes are truly lateral with rounded edges). The measured levels of sub-visible particles are very low at <30 particles of 10 microns and <1 particle of 25 microns, well below the Pharmacopea limits and levels of concern. A comparative study between glass vials and closed vials showed that total sub-visible particles level from the closed vial, as seen by the patient receiving the product, is lower than from the glass vial. Repetitive piercing with the same needle did not show any build-up of particles over time, not even at the 5 microns size. This was observed by sampling 25 vials after several intervals of 1000 piercings and counting particles in those sets of sampled vials.

The needle hub is secured to its base by a cone to cone Luer Lock fitting, complying with the ISO norm 594-2.[1] A small precalibrated torquemeter tool is used for that. Overpressure in the vial is vented through four longitudinal grooves along the needle shaft. Sufficient venting and overpressure depletion is mandatory to avoid any droplet emerging from the needle at withdrawal. The center of the elastomer stopper behaves like a membrane (2 mm thick, 0.0785") that literally wipes the needle as it is withdrawn, leaving it free of micro droplet. High speed video was used for assessing and fine tuning the above process. Accuracy of filling volume was determined to be identical to the one experienced with standard open vials, using peristaltic pump or volumetric stainless steel pumps.

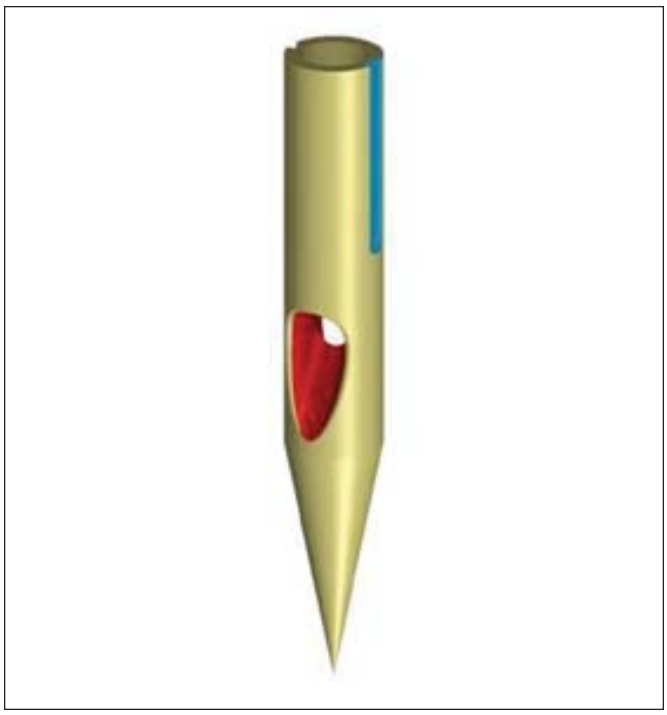

Figure 4. Needle design.

The filling needles are assembled on the needle holder and steam sterilized as an assembly in a Rapid Transfer Port (RTP) container, ready for docking to the barrier. In this way, all components located above the vial in the critical area where filling takes place are steam sterilized before entering the barrier.

Laser Resealing

A semiconductor diode laser with a wavelength of 980 nm has been identified as the most suitable laser source for resealing the TPE stopper, as it does not require any utilities such as gas, cooling water etc. The laser diode is compact and cooled by a Peltier unit. A basic consideration is to use all power coming from the laser as it crosses the TPE thickness of 2 mm. This was achieved by very precisely adapting the absorption coefficient of the TPE at 980 nm. The power of the shot is about 6.3 Watts for 1 second. Another basic consideration is the spreading of this power over the surface needing resealing so that puncture area is fully covered by the laser spot. With the 2.4 mm diameter of the needle, this translates, after consideration of tolerances, to a circular reseal area on the TPE stopper of 4 mm (0.157") diameter. This is achieved by use of a special optical system (not just a collimator) designed to provide a "flat top" power curve covering evenly the 4mm circle.

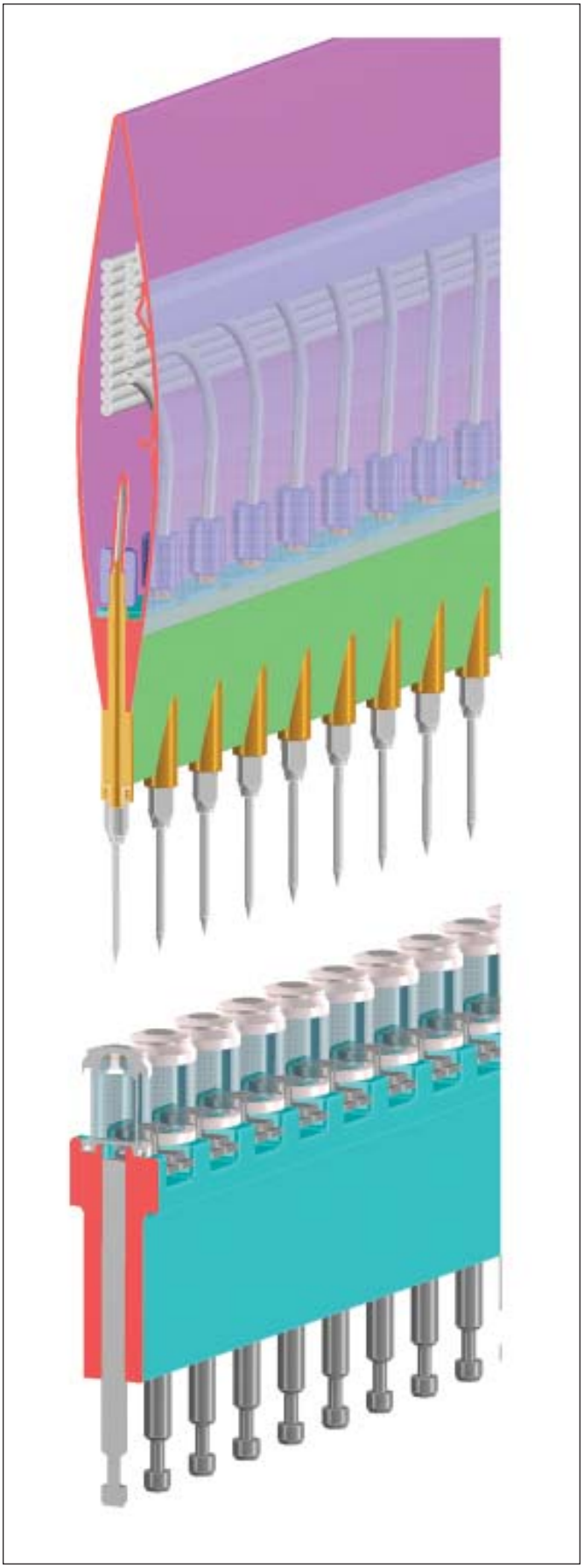

Figure 5. Filling of the closed vial.

The last consideration is to ensure that sufficient material thickness (in this case a minimum 0.3 mm = 0.012" depth, average is 0.5 mm) is effectively re-melted. This is assessed by measuring the cross section of the piercing spot after verification of the elongation under traction of the remelted thickness. This resealing is achieved with a peak temperature at the surface of the stopper (in this case, 165°C) just above the re-melting temperature of the TPE. Under these parameters, the bottom surface of the stopper will see only 38°C for a few seconds, when the heat wave is reaching it, 8 seconds after the 1 second laser shot.

A visible (red) laser spot (less than 1mW) permits checking the centering of the laser spot on the stopper. Controls are developed as follows:

- A power meter (calorimeter type) is used to calibrate the laser (linear characteristic of diode current versus power delivered).
- Daily checks are using the same power meter, and correct centering also is checked.
- Every shot is controlled by an optic fiber, which takes a power measurement at the optical system, which is the last point before the stopper. This ensures that every vial gets a shot with an adequate power level. Any deficiency of the fiber, its connections, or other item would be picked up by this feedback.

Very strict safety measures are taken, complying with International Safety Standards[2] applicable for this laser so that the laser equipment is usable by the operator under a Class 1 safety level (same class as fully encapsulated laser systems).

Capping

The cap is made of High Density Poly Ethylene, using a design that makes it very easy to snap fit over the rounded top ring (self alignment). The cap is not fragile like the aluminum caps and capping does not require precise control of machine settings and tight control of pressure: the cap is just pressed down to a given height above the top ring. In this way, the height tolerance of the vial does not play a role. Vial closure integrity is present from the beginning in the empty stoppered vial assembly. There is no risk of stopper being improperly seated on the vial and no risk of stopper lifting between filling and capping.

Vial Conveyor System

The design of the conveyor system has been based on the following three principles:

- The conveyor system and its dynamic must be designed to comply with the requirements of the working stations.
- The system must have minimum interference with the laminar flow and not cause turbulences above the critical upper part of the vial. Friction must be kept at a minimum and away from the vials.
- The system must allow flexibility for various vial sized formats and speeds, and be capable of easy changeover to accommodate various size vials.

Requirements for the stations are as follows:

- E-beam: high speed single lane continuous movement (for a small e-beam window) with very precise speed and distance to the e-beam source.
- Filling: accuracy of positioning and stability during filling needle movements (avoidance of vial lifting during needle withdrawal).
- Laser: accuracy of position to ensure coverage of the piercing spot.
- Capping: it takes advantage of the easy self-alignment property of the cap on the rounded top ring and of the simplicity of the snap fit assembly. Vertical accuracy is the important parameter for the snap fit assembly. The capping equipment avoids the complexity of multiple head turret with vertical movements.

Here are the resulting basic configurations and design concepts:

- E-beam unit: at the level of the e-beam unit, the vials are suspended using the underside of their top ring, thereby ensuring a very accurate positioning of the height of the vial top surface which will be sterilized. Vial assemblies move under the irradiating window in a high speed single lane with continuous movement supplied by a belt with pushing tabs.

- Filling station: for filling under stable conditions, the walking beam principle has been avoided and replaced by an intermittent motion concept which allows filling of several vials in parallel. Vials are carried by a strong transversal beam using a short (140mm, 5.5") stroke movement.

- On the supporting beam, vials are positioned with accuracy by use of the conical shape on the bottom of the vial that is pushed downward on a centering cone on the supporting beam. Accuracy is higher than a star wheel and the vial body is untouched.

- The beam also is precisely stabilized at the filling station by centering it using cones at the two ends of the beam. A vertical force is applied on each individual vial holder for a secure locking of each vial in a precise position. The center of the beam is supported at the filling station to avoid any bowing of the beam (vertical piercing force is about 10 Newton's per needle).

- Conveying system: transition between the single lane, continuous motion (e-beam) and intermittent parallel movement (filling) is best achieved by a belt with moving pulleys. This provides full flexibility for multiple speed situations with various stopping times for a variable number of vials to be transferred. This system is driven by one continuous speed motor and a driven table for the alternating movements. Both have servo motors.

- Laser station: the laser has to precisely match the piercing point of the filling needle. In order to accomplish this, the same clamping system is duplicated at the laser station. The laser heads are static to avoid any risk of optic fiber damage. Tolerances of the various elements have lead to the requirement for a 4 mm diameter laser melting area when using a 2.4 mm filling needle.

- Capping station: at the capping station, a continuous one lane single station was found to be the best option. The solid plastic caps are easily oriented in a centrifuge bowl, using a natural orienting system based on the shape of the cap. Vertical accuracy is achieved by strongly supporting the vial under the top ring skirt, thus avoiding differences in vial height tolerance (body and bottom ring).

Advantages of the Closed Vial Line Over Isolator Lines

Advantages Derived from the Vial Design

The closed vial is the first clean, sterile ready to fill vial. From a user standpoint, it has the following advantages over glass vials:

- It is resistant to breakage.
- It has an aseptically protected piercing target that is wider than usual.
- It is mechanically very stable.
- It does not contain any silicone.

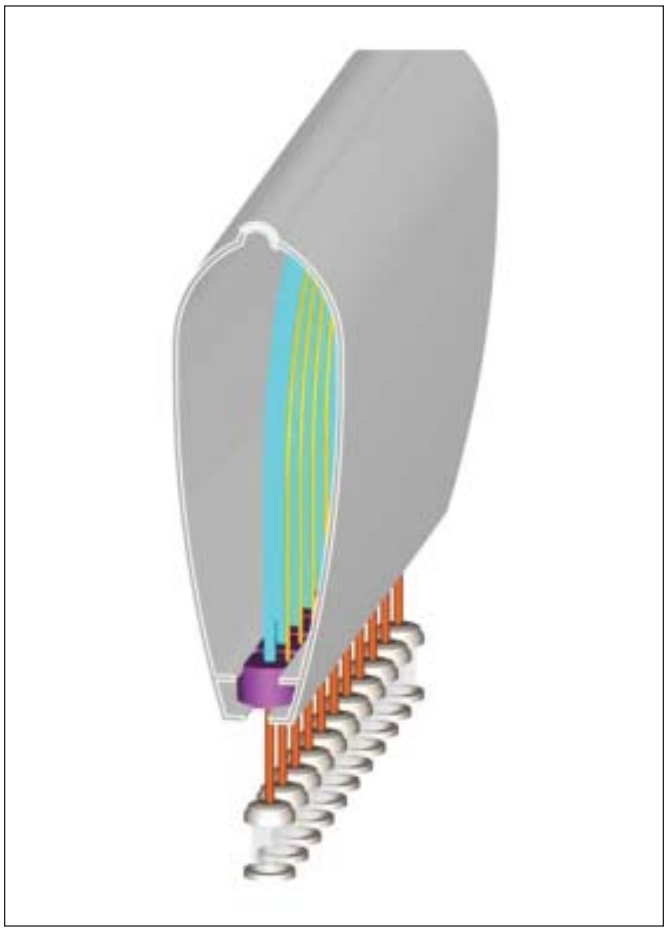

Figure 6. Laser re-sealing of the closed vial.

- It has a very low sub-visible particles level, and no risk of eventual glass particles.
- It has a very low residual volume (average 3 microliters of WFI, compared with 12 microliters for a siliconized glass vial of same content), also a cost advantage in some cases.

Advantages Associated with GMP

From a GMP standpoint, a quick and simple risk analysis shows that the internal sterility of the vial is not exposed during the long track of a classic filling line, from the (sterilizable) cooling zone of the sterilizing tunnel, onto the vial buffer system (with a relatively long exposure time), at the first weighing station, under the filling needles and moving tubings, and at the stoppering. It is to be kept in mind that HEPA filters are not sterilizing filters and that particles are present in an isolator.

The stopper also has a long exposure time and long track between sterilization and placement in the vial: typically it is dropped into the hopper, sorted by vibrator (particles!), travels on the feeding tracks, and gets inserted by the stoppering head.

For these reasons, the added protection of the internal sterility of the vial assembly permits filling operation under RABS, while still keeping a barrier from the operator by use of glove ports and RTPs. This RABS is located in a Class C room similar to the isolator situation.

Risk of stopper lift between filling/stoppering and capping is eliminated.

The bottom of the vial is elevated, a good situation for particle inspection (heavy particles are settling down very quickly there).

Advantages Associated with Reduction of Cost and Complexity

Elimination of very substantial costs and complexity associated with a vial washer, a hot air vial sterilizing tunnel, and stopper washers and sterilizers. Water for Injection associated with those washing processes is spared. Lots of cleanroom space is no longer needed (about 50% factor).

On the aseptic filling line, the stoppering station is eliminated, reducing process complexity. An added benefit is the reduction in line stoppages caused by malfunction of the stoppering equipment and leading to operator interventions (a GMP advantage as well).

The complexity of ensuring Vaporized Hydrogen Peroxide cycle control, an adequate airflow, and overpressure balance in a closed isolator is eliminated. On the other end, it is evident that the cost of the ready to fill vial is higher than an uncleaned glass vial and closure system.

Current Status of Development and Validation of the Closed Vial Filling Line

Vial manufacturing has completed process qualification batches.

Three filling lines are built: one line with a single head filler, and one with two heads (3,000 vials/hour) for filling clinical lots. The third line is a high output line shown on Figure 1, scaled down to a 6 pumps/6 lasers, but the same design allows up to 24 pumps and an output of up to 36,000 (2 mL) vials per hour. The first large output production line is planned for delivery in 2007.

The single head equipment is nearing completion of a full validation. Three fully successful media runs of 6,000 vials each have been performed as a concept study on the single head line still located in the workshop, confirming the robustness of the aseptic process. Filling of biological products for stability tests are ongoing.

Vial manufacturing capacity is being scaled up to 40 million/year from a first vendor, and plans are to have multiple sourcing in the near future. Developments are ongoing for a closed syringe and a closed vial suitable for freeze drying.

Conclusion

In summary, the closed vial technology is believed to become a new standard for the aseptic filling of liquid pharmaceutical drugs, because of the improved quality of the aseptically processed drugs provided to the patient, and because of the significant reduction of the cost and complexity for the manufacturers.

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Acknowledgements

Core technology has been licensed from Medical Instill Technologies Inc.

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PHARMACEUTICAL ENGINEERING Interviews Norikazu Eiki, President and Representative Director, Bayer Yakuhin, Ltd.

This interview was conducted by ISPE International Regulatory Affairs Advisor, Joe Phillips, ISPE Board Member, Shinichi Osada, and Pharmaceutical Engineering Editor, Gloria Hall.

Norikazu Eiki joined Ciba Geigy in 1979 as a Mechanical Engineer. He joined Bayer Yakuhin in 1994 and became President in 2002.

Q What experiences prepared you for your current position?

A I've had a quite unique career in the pharmaceutical industry. In 1979, I joined Ciba Geigy as a Mechanical Engineer to develop their antibiotics product. Then I moved to the Engineering Department and began focusing on constructing pharmaceutical facilities in South Korea, Singapore, and Hong Kong. Then I was transferred to Ciba Geigy in Basel, Switzerland. I became President of Bayer Yakuhin in 2002 and am the first President with a mechanical engineering background in Bayer.

Q When was Bayer Yakuhin founded? What products do you currently manufacture and in what therapeutic areas?

A Bayer Yakuhin Limited, referred to as BYL, was founded in 1973. Yakuhin means pharmaceuticals. Bayer Yakuhin is dedicated to the development of CardioVascular Risk Management products. The biggest product in our line is Adalat. Next is a diabetics product, Glucobay. The third is Kogenate, a hemophilia product. Bayaspirin is an antiplatelet product and Ciproxan is an antiinfective. We recently launched Levitra, an erectile dysfunction treatment product in Japan. These are the major products of Bayer Yakuhin at the present time.

Q What factors do you believe have contributed most to Bayer Yakuhin's success and growth in the pharmaceutical industry?

A Good products, good reputation, and good people all contribute to our success and growth. Bayer Yakuhin is a well established and reputable company with more than 100 years of history in Japan. We have long and good relationship with Japanese wholesalers and medical societies. Therefore, although it is a foreign-affiliated company, Bayer Yakuhin is almost like a Japanese pharmaceutical company. We have very sound and solid products. Adalat was launched in 1976. That was 30 years ago, and Adalat has been among the top 20 best selling pharmaceutical products in Japan. Also, I can say we have very dedicated people at Bayer Yakuhin.

Business Strategies/Vision

Q What are some of the major barriers you and other pharmaceutical manufacturers face globally?

A I believe that some of the major barriers in the pharmaceutical manufacturing industry include less incentive for doctors and patients to conduct/participate in clinical studies, price cut pressure from the government, political pricing, and long development period. Economically, we have price cuts every two years. Pricing for new products is not totally clear to the pharmaceutical industry. Today, we are still facing the problem of long new product approval processes. This period makes the Japanese pharmaceutical company look less attractive when foreign companies analyze the Japanese market.

"Good products, good reputation, and good people all contribute to our success and growth."

Q What is your strategy for long-term growth?

A Bayer's strategy for long term growth includes strengthening the product pipeline through internal R&D and licensing, establishing strategic alliances for specific products focusing on selected therapeutic areas, investing in people, and promoting innovation and improvement in all areas of operation.

Q What do you see as the major growth area for Bayer Yakuhin?

A CardioVascular Risk Management (CVRM) and Specialty Care (Oncology, Hematology, and Cardiology) are the major growth areas for us.

Q What are some of your challenges in Japan?

A It has been challenging trying to build a strong Oncology platform in Japan.

Q Are these challenges different than with Bayer US?

A Yes, Bayer US is focusing on Specialty Care pharmaceutical products. Zetia, in collaboration with Schering-Plough KK (SPKK), is unique to Japan.

About Bayer Yakuhin

Number of Employees
1,450 as of April 2005

Sales in 2004
$ 693 million / 797億円
($1 = 115 円)

Major Locations and Functions
- Head Office in Osaka
- Factory in Shiga Prefecture
- Distribution Center in Osaka
- 11 Regional Offices
- 82 Field Offices

Partnerships and Acquisitions

Q What is the long term vision for Bayer Yakuhin? How would this vision differ (if at all) from the biotech industry?

A We envision ourselves as a CVRM Company that has a unique product line with a portfolio of drugs that control hypertension, hyperglycemia, hyperlipidemia, and blood clots. Our vision also includes harmonizing with Bayer's DS business group and operating our Oncology business through unique strategies.

Q Have Bayer and Bayer Yakuhin made any acquisitions or partnerships over the years?

A We will be co-marketing Zetia with SPKK in Japan. Globally in the development area, we are collaborating with Zilip-Pharma for Long-Acting Kogenate, with Onyx Pharmaceuticals for Sorafenib, and with Ortho-McNeil for Factor Xa-inhibitor.

As I indicated earlier, the long-term strategy of Bayer Yakuhin is to strengthen our product pipeline through R&D, our licensing strategy, and our strategic alliances in the therapeutics areas.

Q How did these acquisitions or partnerships contribute or influence your success?

A We believe that strong strategic alliances in marketing and development will help improve Bayer's performance and shorten product development time. We have demonstrated experience with global alliances, including partnering with Schering-Plough (US and Japan). And also the major focus area for Bayer Yakuhin is CardioVascular products. More than 50% of our turnover comes from this franchise. This is our long-term vision and the product strategy of Bayer Yakuhin.

Growth/Expansion

Q Are there any major differences between facilities in Japan, Europe, and the US?

A Yes, I think the facilities, the requirements for the facilities, as well as the application documents are quite different.

Q Can you discuss some of the future strategies you are planning?

A The CardioVascular franchise is our primary focus as we prepare for the future. Bayer Yakuhin is investing highly in the future of its Cardiovascular, Oncology, Hematology, and Cardiology franchises.

The good harmonization we have with our other business units, including diagnostics and diabetic care, is unique. We can harmonize with other divisions combining with our drug and pharmaceutical business.

Leadership Style

Q What is your leadership style?

A I focus on the so called 3C plus E, or Change, Challenge, Communication, plus Execution. I especially value the importance of communication because it is the key to motivate the employees. My unique practice is to have the so-called President's roundtable meeting with all of our employees. I visit the manufacturing and sales offices. We have 82 sales offices all over Japan and some 1500 employees. I have covered two-thirds of direct communication with our employees so far.

Q Are you investing in productivity improvements in your facilities?

A Yes, we promote small-group activities, Kaizen activities, and sales efficiency activities.

Q What are some of the key metrics used in your organization to gauge business performance or success?

A We analyze sales, profit, market share, and sales growth rate. We have clear key metrics to measure our profitability and business performance. Of course, we look at our sales turnover and also the important thing is our profitability. The other cash flow management is the inventory-days on hand management, and accounts receivable management is one of the important management keys. From the production side, we measure the cost of goods manufacturing trend and the inventory days on hand by product. This would be divided by the costs of the manufacturing processes starting from dispensing, compressing, granulation, and coating – all of the processes we have at this inventory are analyzed with Key Performance Indicators (KPI).

Q How do you measure performance in manufacturing and other areas?

A Other than the usual indicators like manufacturing quantity, inventory, budget control, and others, we try to quantify the quality of our performance by evaluating the number of technical complaints, using the Right It First Time (RIFT) ratio.

Manufacturing/ Development/Marketing

Q What do you see as the challenges or barriers to achieving the goals that Bayer has set for its global pharmaceutical and biopharmaceutical manufacturing operations?

A The goal is to be competitive enough to survive as one of the Bayer global manufacturing sites. We should be one of the unique pharmaceutical operations, especially for manufacturing, not only for the manufacturing cost, but also for quality and delivery. So the three major important factors in our manufacturing facilities are cost, delivery, and quality. These three are clearly the most important for our manufacturing for the future.

Shiga Factory.

Q What technological and operational breakthroughs do you anticipate within the next five years in the pharmaceutical and biotechnology industry?

A I think the industry will go for the biotechnology side and unique long-acting hemophiliac products. Currently, our hemophiliac program requires patients to inject this product quite often. In collaboration with Zilip Pharma, a US company, we are in the process of developing a longer-acting hemophiliac product. This is quite a unique joint technological development that will give us an opportunity to improve the quality of life for some of our hemophiliac patients.

Regulatory, Quality, and Political Concerns

Q What impact does the Ministry of Health, Labour and Welfare (MHLW) have on your operations in Japan or globally?

A The MHLW has a significant impact on pricing, approval, and regulatory issues relative to our business in Japan.

Q What impact do you think re-importation will have on your business (if any)?

A Re-importation is not a major issue in Japan. However, due to the development of IT, some individually imported drugs are coming to Japan through the Internet.

Q What is Bayer Yakuhin doing to reduce or manage risks from bioterrorism?

A We have a well secured repository system.

Q How is Bayer Yakuhin addressing the security issues of product distribution? Are you implementing Radio Frequency Indicators (RFID)?

A We have not used RFID, but control the logistics with a barcode system. Levitra, especially, has to be handled on the same security level as stimulant drugs so we've included a hologram on the product package to prevent counterfeiting.

Future Industry Directions and Trends

Q What are your biggest concerns for the future – if any?

A The concern for the industry is the longer approval period because sometimes we have to employ our people to launch new products based on expectations. When the product launch is delayed for some period of time – say one year or six months – that's an impact on us. The efficiency of product approval from the PMDA and also the MHLW is one of the concerns for the industry. Another concern is the pricing of new products. This is not clear enough to the pharmaceutical industry. This should be better defined in the future.

"…the long-term strategy of Bayer Yakuhin is to strengthen our product pipeline through R&D, our licensing strategy, and our strategic alliances in the therapeutics areas."

ISPE's Role

Q Do you see any role that ISPE can play in working with the industry or providing forums or conferences – is this helpful?

A Yes, I am expecting a lot when it comes to the current and future role of ISPE. We are expecting a lot from ISPE's global training. We also look to ISPE to provide the benchmarking for the pharmaceutical industry, especially for productivity and regulations. Benchmarking could be an important initiative for ISPE, now and in the future. We anticipate what ISPE is expecting for PAT and also risk management–based activities. This, I am sure, will soon be implemented and accepted by the Japanese pharmaceutical industry in the future.

Q Anything else you'd like to say to the readers of *Pharmaceutical Engineering* – from a Bayer perspective?

A Pharmaceutical Engineering will continue to play an important role for the industry not only as it relates to manufacturing technology, but also from the engineering viewpoint for companies to remain competitive in this marketplace. I am expecting a lot in the way of proposed Pharmaceutical Engineering curriculum, which could be implemented in the universities in Japan. As I've talked with several Japanese universities, they expressed a lot of excitement with regard to developing curriculum geared toward Pharmaceutical Engineering. Japanese universities will introduce within a few years from 4-year course to 6-year pharmaceutical department course. They'd like to add some value for this extended 2-year course. So we are really expecting major Japanese universities to introduce Pharmaceutical Engineering curriculum in the Pharmaceutical Departments.

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Operational Qualification (OQ) Testing of Integrated, Automated Systems

by Poul Grav Petersen

This article describes the challenges in planning, executing, evaluating, and reporting OQ activities upon a brief introduction to OQ for automated systems.

Introduction

OQ of automated systems for pharmaceutical manufacturing provides particular challenges in terms of coping with a complex assembly of facilities, equipment, and software, usually supplied by different suppliers. Being one of the final activities of a project, OQ will often be subject to a tight schedule, and this merits careful test preparation, efficient test execution with clear objectives, and competent processing of the test results. Effectively executed, a successful OQ will provide the pharmaceutical manufacturer with confidence in the subject for qualification, and the qualification documentation will be available for demonstrating compliance with GMP requirements.

Current automated systems for pharmaceutical manufacturing are usually an integration of sub-systems and components from several independent suppliers. Figure 1 shows examples of a few general architectures, where the higher levels Manufacturing Execution System (MES) and Supervisory Control and Data Acquisition (SCADA) define the job to be done and report on the results, while the lower levels Distributed Control System (DCS) and Programmable Logic Controller (PLC) control the equipment in the plant. The suppliers of such systems may range from software houses with limited pharmaceutical experience to traditional pharmaceutical suppliers with limited automation experience.

The integration of the individual supplies should take place gradually during the implementation project as the components become available, but it may not be possible to have all components available for integration with each other and with the controlled equipment until the final commissioning and OQ are scheduled to start. At this stage of a project, the schedule is usually tight and a project will be subject to considerable pressure to complete its activities as scheduled and to cope with delays that any of the suppliers may have experienced. Thus, the commissioning and OQ activities need to be carefully planned in order to gather and process the information within the time slot available and still fulfill GMP requirements.

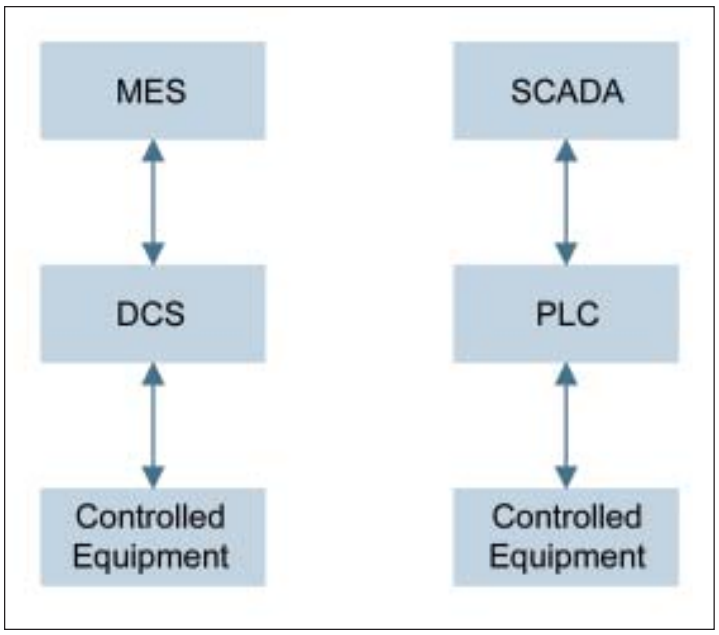

Figure 1. Example architectures of integrated, automated systems.

The ISPE Baseline® Guide for Commissioning and Qualification[1] identifies the life cycle activities to be performed, particularly emphasising the importance of impact assessment. The impact assessment offers the suppliers the option to focus their qualification efforts on functions with direct impact. However important the distinction between direct impact, in-

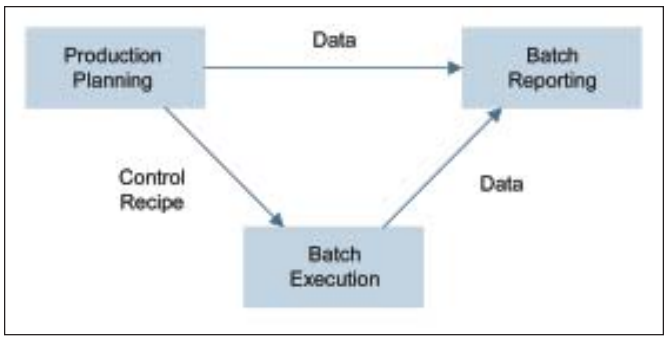

Figure 2. Typical functions to be tested.

direct impact, and no impact is, it will still need to be applied using common sense. As an example, a direct impact function and an indirect impact function may require essentially the same test scenario to be set up for the automated system, so rather than doing this twice, it will be beneficial to let the qualification cover the direct impact function as well as the indirect impact function. The implication is that the qualification activities achieve primary importance compared to the commissioning activities. Furthermore, as the functionality of a system, which is an integration of automation and equipment, is provided through the automation, the OQ of the automated system will tie together the efforts of several suppliers. However, this does not imply that qualification activities for the individual supplies are less important, merely that the full functionality will be achieved only through the automation.

This article is based on experience from several projects ranging from small stand-alone applications to integrated solutions for large facilities and including API processing as well as finished pharmaceuticals.

Automated Systems and OQ

An automated system provides a mean to perform tasks repetitively and with the speed, accuracy, and reliability that surpasses the level human beings can achieve. Automation is a key element in current pharmaceutical manufacturing, but the level of automation has rarely exceeded the level where operators are indispensable. Thus, the automated system may be seen as an interface between operators and the physical equipment in the plant. It relieves the operators from manually operating valves, motors, pumps, etc. and it will usually do the same things over and over again. It provides insight into the performance of the equipment through instrumentation, and through logs of measurements and operator interactions, it allows subsequent review of the process performed by the equipment.

In order to use an automated system for pharmaceutical manufacturing, the regulatory authorities require documented evidence that the system actually does what it is intended to do. Requirements must be stated in specifications, sound engineering principles must be applied throughout design and development, and a thorough series of tests must be performed and documented prior to commencement of operation. The final set of tests concerned with the operation is termed Operational Qualification (OQ).[1]

The automated system presents for the operator an interface to the process performed by the controlled equipment. OQ should concentrate on this interface, both as a means for providing input to the system and as a device for presenting output from it. A set of typical tests will have to ensure that the operator can operate the equipment from this interface and that it is possible to monitor the performance of the equipment via the interface. This may include:

- Control recipes may be generated.
- Operating sequences perform as specified.
- Legal values may be entered and illegal values are refused.
- Control loops are stable within their specified operating range.
- Alarms are generated as required.
- Calculations are correct.

Equally important, another set of tests will have to ensure that the data generated, stored, and presented by the automated system is valid. This may include:

- Correct data is collected.
- Data is secured against loss and corruption.
- Data presentation in reports and trend curves is correct.

Test Preparation

The intent of OQ is to verify that the system fulfills specified requirements. Thus, it is tempting to go ahead and set up test conditions where each requirement will be addressed in turn. For automated systems, it is strongly recommended not to use an approach like this. Either some parts of the software will be exercised several times as part of setting up test conditions, or the test will be performed in a localized manner, where the test demonstrates that the tester is able to bring the system to a state where fulfillment of the requirement may be shown, rather than demonstrating that the requirement is fulfilled in an operational context.

Instead test planning should adhere to the operational work flow and the design of the system. Tests should be devised such that they cover normal operation (exercised to its limits) as well as exception handling. The specified requirements will still be the basis for the test, but they should be addressed in the operational context where they are relevant. Cross referencing the requirements to the tests is crucial since one test sequence may address many requirements. In the extreme, it may be possible to cover all requirements by just a single run of each operational sequence (recipe, procedure, operation, phase etc.), but some tests may leave the system in a state where normal operation cannot be resumed, therefore requiring several runs of an operational sequence.

Minimizing the number of tests is important in order to comply with the required schedule. Equally important, the gathering of information during the tests should be optimized. Of course, the test preparation must ensure that the information is sufficient for documenting fulfillment of the

requirements, but additional information may be required or beneficial. An implicit requirement (if not explicitly stated) is that reporting facilities such as trend curves and batch reports included in the automated system should be verified. Even standard packages should be included in the verification as an element of customization is always present. This verification will usually require information to be gathered throughout the test, and it requires a close scrutiny of the procedural part of the design to identify each piece of information and when it will be available for collection during the execution of the tests.

Careful OQ test preparation will usually reveal a number of errors otherwise to be disclosed later during the actual tests (and then substantially more expensive to correct). Errors may be found in the design of a single entity, but it is much more likely to find them in the interaction between entities. Thus the test preparation should focus on the functionality to be provided by the integrated entities, rather than concern itself with excessive details of single entities. The person or team preparing the test would be well advised to put themselves in the position of the prospective users.

Test preparation is a challenging effort where the required skills include understanding the business process, details of the pharmaceutical process, the automation architecture, as well as the most recent software innovations – all seen from the perspective of achieving regulatory compliance.

The result of the test preparation is an OQ protocol as described by the ISPE Baseline® Guide for Commissioning and Qualification.[1] Depending on the size of the system, it may be organized in several separate protocols and reference a number of attached test specifications, test plans, test scripts, etc.

Test Execution

The approved OQ protocol forms the basis for the tests to be executed. The protocol will usually state the prerequisites for commencing OQ, and they may include:

- precautions to ensure safe operation of the equipment
- checks on the availability of documentation, including specifications, system documentation, and applicable draft SOPs
- identification of the items to be tested using a configuration management scheme
- completion of other test activities (FAT, SAT, commissioning, IQ, etc.)
- identification and availability of test materials

Beyond fulfilling such formal prerequisites, it may be an advantage to perform informal dry-runs of certain parts of the specified tests. This will serve the dual purpose of familiarizing the test personnel with the protocols and the test items, and of weeding out errors from the system which do not manifest themselves until the integrated system is operated under realistic and controlled conditions. The formality imposed by following a strict protocol will quite often reveal information on problems which have passed unnoticed even during the commissioning. Any corrections of errors still should be subject to the change control applicable at the moment, but the formality, and consequently, the cost will usually be less if they are performed before the formal qualification.

According to the recommendation above on structuring the test according to the work flow, one of the first parts of the test will be concerned with the features for planning the operations on the system - *Figure 2*. The result of the application of such features is often termed a control recipe, and they may include editing master recipes, handling of material master data, production scheduling, control recipe generation, etc. These features are all worthy subjects for test in their own right, but they are even more important to exercise in order to set up the framework for the tests to follow.

Tests under realistic conditions are best performed in the context of a control recipe. The simplest test specification will be just to press the start button, and then make observations on what happens. The complexity of contemporary automated systems requires the test specifications to be more elaborate than this, but the tester interventions should be kept to a minimum. Ideally, the interventions should be constrained to normal operator interactions (with due challenges), but there will be requirements where it is necessary to force the system into a state which will not occur during normal operation. The reason for recommending this approach is that the test should be concerned with evaluation of the system rather than the ability of the tester in setting it up.

During the test, observations should be made as stipulated by the protocol or the test specifications included in the protocol. The use of screen dumps (print outs of the data and graphics displayed on the operator console) is a valuable option, but it should not be exaggerated. The value of test documentation depends not only on accuracy and detail, but also on comprehensibility. The test documentation should not develop into a user guide with screen dumps for every key stroke – particularly for intensive operator dialogues, excessive use of screen dumps appears to be a misunderstanding of their value.

For systems where real-time aspects are involved, the situation is somewhat different. It may be extremely difficult and stressful to perform such tests, and sometimes the timing permits the tester to do nothing more than to decide when to make screen dumps. Such screen dumps are a valuable asset, but there will be a need to select the ones to include in the test documentation – those that do actually show the system behavior and the fulfillment of requirements.

Beyond taking screen dumps, the test personnel should record the observations they note, and in particular, the interventions they make. In current automated systems, the logging facilities are usually so elaborate that it will be possible afterward to see that something has been done by the test personnel. It will be very helpful in analyzing the data to have additional information from the test personnel on what they have done and on what the aim was.

While executing the test, the test personnel should be reluctant to evaluate the test results. Obvious non-conformi-

ties have to be handled as per the protocol, but apart from such situations it may be quite difficult to see errors as they occur, let alone to detect the cause of the error. Automated systems are complex and so are the errors that may appear.

It is generally accepted that tests should not be carried out by the persons who have participated in the development of the test item. However, the complexity of some items may be so high, that a person unfamiliar with an item will be incompetent to carry out the test or spend an exorbitant amount of time in preparation. In this situation, it may be possible to compensate for the "blindness" of the developer towards his/her own errors by allocating an observer and/or increasing the review of the test results.

It may be an advantage to get the operators involved in carrying out the tests. For new facilities, OQ will be one of the first opportunities to get familiar with the facility and there may be a fruitful cooperation between engineers involved in the supply of the facility and its future operators. For renovated facilities, the operators will have an in-depth knowledge of the facility which can contribute significantly to a smooth test process.

Processing of Test Results

The test execution may create an overwhelming amount of data. The test personnel must organize these data such that they constitute readily available GMP documentation. The OQ protocol and company specific guidelines should include details on current requirements for GMP documentation.

As part of this processing, non-fulfillment of requirements and deviations from expected behavior as expressed by the protocol should be identified. Some non-conformities are obvious, while the detection of other deviations requires an in-depth knowledge of the facility. It could be argued that the OQ protocol and the test specifications included in it should provide a clear answer on where non-conformities have occurred, and to a certain extent that is true. However, bearing in mind the complexity of an automated system, it would be naïve to expect the protocol to describe every aspect that is relevant for the system. The test personnel should employ their competence (and professionalism) to evaluate the test results with the aim of detecting those situations where the system does not meet the user expectations. Care should be exercised not to let new user requirements creep in at this late stage – as an aside, user representatives should be just as concerned about this as the supplier since it will cast serious doubt on the validity of the user requirements.

It is difficult to provide general advice on how to find errors, but it is always interesting to diagnose unexpected situations (e.g., the occurrence of alarms and warnings), even if they are not directly related to the test being performed. It also may be worthwhile to follow information across system and sub-system boundaries, especially where different suppliers are involved, different technologies are applied, or different development groups have been working.

If the system includes reporting facilities (e.g., generation of batch reports), the test results should be used to verify the reports - *Figure 2*. This verification should be included in one or more separate test specifications, where the results from test execution on the system are used to verify every piece of information in the reports. This verification is where you really benefit from executing the test under as realistic conditions as possible. You should be able to follow data throughout the system from control recipe generation through execution on the controlled equipment to the generated report. This verification is extremely important, particularly since experience shows that this verification is one of the activities that reveals most errors. It is not that the reporting facilities are more complex or of poorer quality than other parts, but rather a result of the reports being the point where a lot of ends have to meet.

Once the processing of the test results is completed, the outcome should be reviewed by someone outside the test team. Frequently, the test team becomes so proud of their achievements in actually completing the test, that they forget to look for or simply cannot see errors. A review by someone with an in-depth understanding of the system may be very valuable, and experience has shown that this review will often find more errors than the test team itself has found. Members of the team that prepared the test may be well suited for this job, but it also may be performed by QA representatives – provided that they have the necessary technical background and are not just concerned about formalities.

Test Reporting

The test results should be summarized in a report as required by the OQ protocol or by company specific procedures. The summary should state the conclusions that may be drawn from the test results, particularly:

- Which items (specified by version numbers) have been qualified?
- Which non-conformities were found, how have they been classified, and how have they been handled?
- Are there any unresolved problems, and how will they be handled?
- What is included in the qualification documentation?

The report should be approved by the proper company authorities, which normally will include the person in charge of the manufacturing facility and a representative from the proper QA unit.

Example: OQ Testing for a Simple Storage Vessel

Consider as an example a storage vessel in a pharmaceutical plant. The functions required for the vessel are:

- filling
- emptying
- agitation
- temperature control
- CIP

The Distributed Control System (DCS) is equipped with operator consoles in a control room for monitoring and controlling this unit as well as other units in the plant. Associated with the control system is a Manufacturing Execution System (MES) for handling master recipes and generating and downloading control recipes to the DCS. Both the DCS and the MES interface to a reporting system which generates batch reports including trend curves.

The kernel functions of each of these systems have been OQ tested separately so for this unit the OQ tests may concentrate on how the systems handle this particular unit. The tests involving the physical equipment are divided into three parts related to the operational sequences required for the unit (filling, emptying, and CIP). Each part is performed with parallel operation of the unit that this unit interfaces with:

- for filling the unit that supplies liquid to the unit being tested
- for emptying (one of) the unit(s) that receives liquid from the unit being tested
- for CIP the unit that supplies CIP liquids to the unit being tested

Each part is initiated from the MES with control recipe generation and downloaded to the DCS. For the test, details are recorded on the batch and its parameters, e.g., set points for flow, temperature, level, and agitation speed. The control recipe is executed on the unit and its performance is monitored from the operator console. The protocol specifies the checks to be made while the control recipe is executed. This may include checking valve positions on the route, and the state of pumps, agitators, and PID controllers. To document the test, print-outs of the operator console (screen dumps) are made at several pre-defined moments, and they shall include print-outs for the interfacing units. During the control recipe execution, the control system is challenged as appropriate, e.g., by stopping a pump, by attempting to initiate illegal actions, or by interrupting the supply of a cooling agent. When the execution of the control recipe has been completed, the batch report is printed and its content is verified against the documented observations made while executing the control recipe. To document this part of the test, the batch report is annotated with cross references to the screen dumps made earlier.

The tests of the operational sequences described above constitute the main part of the test. They will be supplemented by a few specialized tests which cannot be performed as part of an operational sequence. Control loops for temperature and flow will be tested in a special test set-up where set points are set to their limits while monitoring the controlled variable. Alarms and data entry for parameters (which are a traditional regulatory concern) will be tested using a combination of actual tests and code review.

Examples of problems found in the qualification of a unit like this are:

- Batch data (batch number, quantity, temperature, pH, etc.) transferred between units are not reported or not reported correctly in the batch report.
- CIP trend curves for flow, pressure, and temperature show that the CIP spray nozzles in the vessel do not work properly.
- The operating sequence for emptying fails to update upon completion the hygienic status for a common resource unit connecting the unit being tested with the receiving unit.
- A valve belonging to another unit generates warnings during the CIP sequence. Analysis shows that the unit is coupled to the same CIP unit as the unit being tested, and that the valve in its closed state cannot cope with the pressure in the CIP pipe.

It should be remarked, that normally the qualification will pass without any major problems, but the examples listed above are from actual projects, where the qualification showed that GMP is not just a matter of producing paper.

Conclusion

This article has described an approach for OQ testing for integrated, automated systems for pharmaceutical manufacturing. The emphasis has been on the qualification of the functionality of the complete system, including automation components at different levels and the controlled equipment. It has been the aim to take the position of the prospective users and ensure that their expectations for the system will be met. However important it is to ensure that all the details of the components of the system meet their specifications, it seems even more important to ensure that the components fit together such that the integrated system achieves its desired functionality.

Current automated systems usually include a reporting mechanism, where data on the operations on the controlled equipment are recorded. As such data are subsequently used for product release it is of utmost importance to ensure that the data constitute a valid representation of operations performed on the controlled equipment, and that the reports extracted are reliable. The approach presented above integrates the verification of the reporting mechanism with the test of other components of the integrated system.

The approach presented here fits well into the framework presented by the ISPE Baseline® Guide for Commissioning and Qualification.[1] As argued above, for automated systems, it is often an advantage to set up a single test scenario where a group of functions may be tested regardless of the result of the impact assessment so the emphasis is on qualification. The approach fits less well with the GAMP Guide for Validation of Automated Systems[2] and the GAMP Good Practice Guide: Validation of Process Control Systems.[3] GAMP emphasizes the importance of testing components of a system at various levels at the appropriate place in the life cycle, and this is a sound and recommendable engineering approach. However, GAMP is less specific on the need for tests of a complete, integrated system where the full functionality becomes available. Experience has shown that it is worth-

while to supplement the tests recommended by GAMP with tests where system and sub-system boundaries are crossed, particularly in projects with many suppliers working under a tight schedule.

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About the Author

Poul Grav Petersen received an M.Sc.E.E. in 1977 from the Technical University of Denmark. Throughout his career, he has been working with software engineering and software quality. From 1977 to 1991, he was with ElektronikCentralen (now DELTA, an independent, non-profit R&D organization) doing R&D in a number of European collaborative projects and consultancy assignments for primarily the Danish industry. From 1991 to 1996, he was quality manager for GN Elmi as (now Nettest A/S, a manufacturer of telecommunications test equipment) responsible for achieving and maintaining ISO 9001 registration. Since 1997, he has been with NNE A/S where he has been working with computer validation, primarily OQ, for a number of pharmaceutical facilities supplied by NNE. Petersen is a member of IEEE.

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The Power of Planning and how it Translates to Commissioning Efforts

by Katie Henchir

This article explores one planning approach for commissioning efforts that divides planning into four categories.

Introduction

Commissioning has evolved to address many of the project lifecycle issues the industry is facing, including those centered on documentation, proper installation and start-up, and general acceptance of a piece of equipment. This initial activity also has allowed many operating companies to expedite project schedules by capitalizing on early project phases through the use of Good Engineering Practices (GEPs) and Good Documentation Practices (GDPs). By the late 1990s, these issues were addressed through the use of a formal commissioning plan and subsequent commissioning procedures.

Today, organizations around the globe are seeking the catch-all solution for Commissioning and Qualification (C&Q) efforts ensuring the proper manufacture of commercial product with limited project delays. Unfortunately, there is no perfect strategy and execution; we as an industry are learning and advancing the concept of commissioning based on experience. From these experiences, commissioning teams devise the best suited plan to move the project forward.

This article discusses one approach to overcoming the many known issues by dividing commissioning preparation into the following four project phases:

- Clarity: When you seek out clarity, you are searching for the definition. As with many other words, commissioning can take on several meanings. This first phase explores the translation of company practices, policies, and programs to define what commissioning means to a specific organization.

- Compass: Your compass is your direction and essentially your scope of commissioning. Your compass combined with a solid definition begins to shape the scope of your commissioning program.

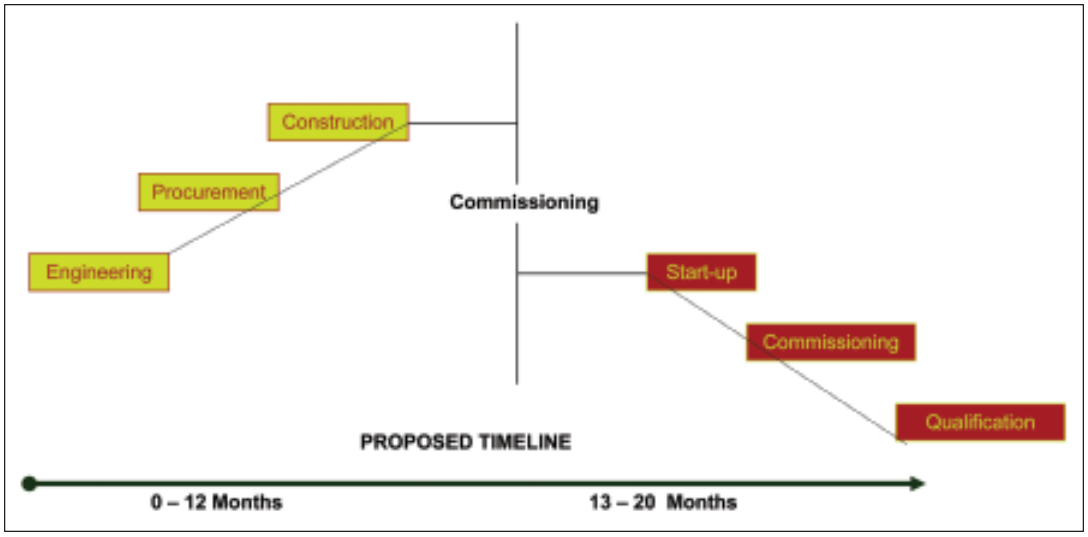

Figure 1. Commissioning-Centric.

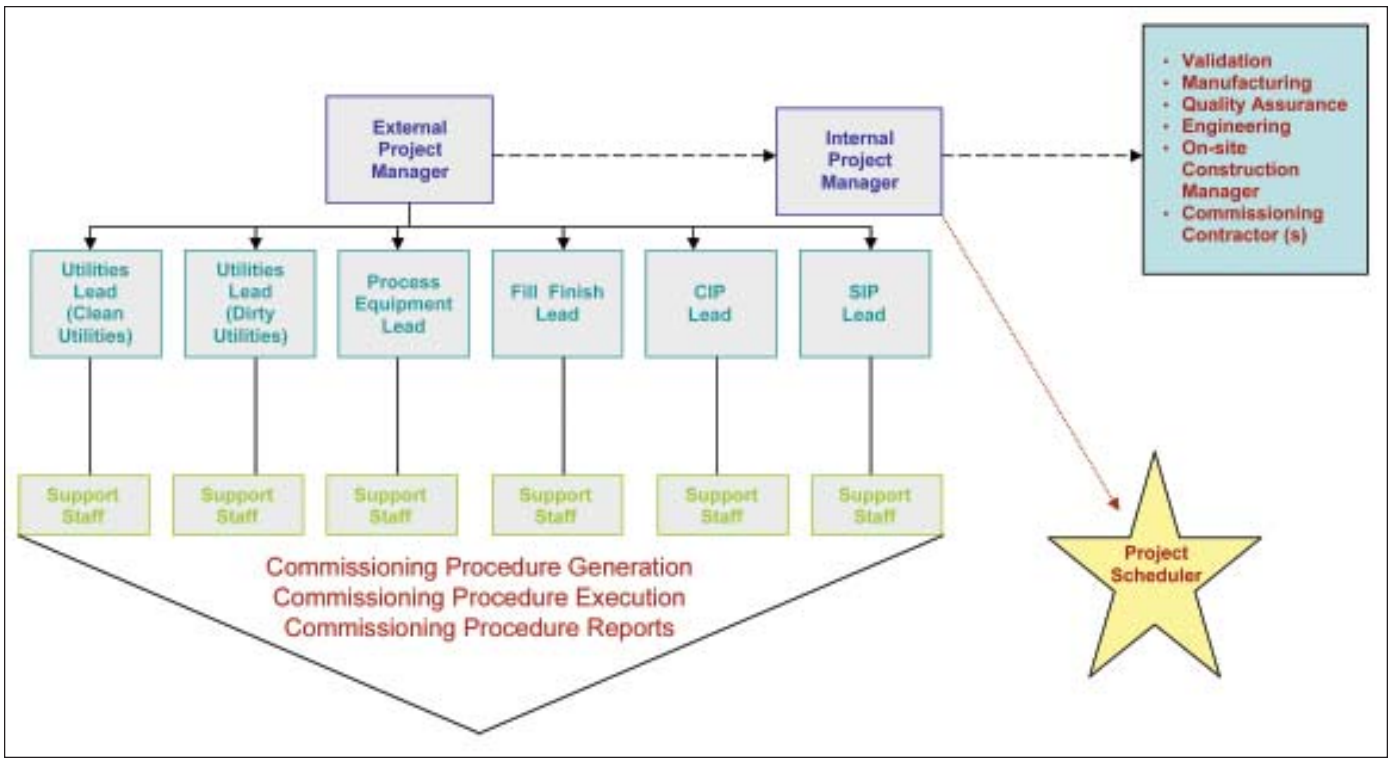

Figure 2. Commissioning team.

- Planning: It's simple. Planning forces a team to think strategically and paint a clear path forward.

- Procedure: A Commissioning Procedure, again, not a new concept, but an evolving concept should be formatted and designed to satisfy the definition of commissioning.

However, the fundamental principle driving this approach is threefold, planning early is a value-added activity; agreement on project approach is critical; and identifying key players on both the client and contract side to remain on the project in its entirety is vital. Lastly, commissioning planning early in the project lifecycle becomes the focal point allowing a project team to plan activities to the left (construction) and to the right (qualification) - *Figure 1*.

This planning exercise is an integrated approach attempting to maximize the benefits of commissioning.

Finding Clarity

Crafting a definition, as simple as it sounds, presents several challenges and is an integral component of success. The following definition from the ISPE Commissioning and Qualification Baseline® Guide published in 2001 is thorough, complex, yet easily adopted and suitable for many commissioning efforts:

> *"A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations."*

The Baseline® Guide definition suggests the following principles:

It's a documented plan. Commissioning activities can be as rigorous or as simple as an organization chooses. Regardless of the methodology, a documented plan is recommended to ensure the success of a project.

Management is critical. Identifying the key team players, internally and externally, combined with management leadership is truly the critical success factor in any project. When the

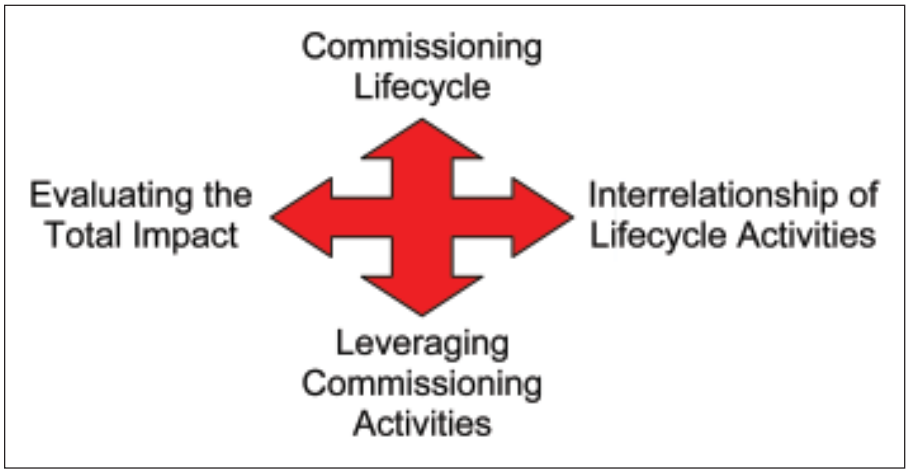

Figure 3. Commissioning compass.

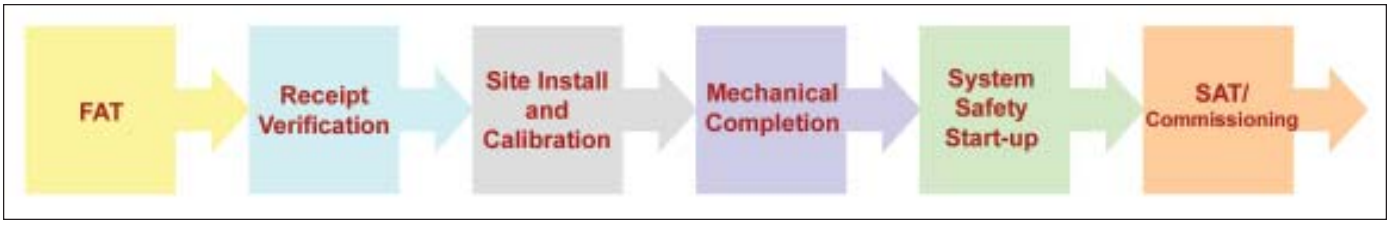

Figure 4. Activities impacting commissioning.

commissioning effort is outsourced, the internal team must first be assembled identifying one representative as the conduit between all parties. The selected firm can join assigning a project manager reporting directly to the internal lead. From this foundation, an infrastructure can be designed to support the effort. A typical Commissioning Team organizational chart should include both internal and external representatives.

Institute sound engineering practices. Good engineering practices must become a way of life. Each equipment and utility design should satisfy the end-user requirements to consistently manufacture a product within a specified range. Good engineering practices promote functionality, reason, and safety.

Appropriate use of start-up procedures and technical support. One of the easiest vehicles to attack this task is to start by requesting a quote for start-up procedures and technical support for all equipment and utilities. At this time, it is recommended to request a sample start-up procedure; the price and the sample procedure truly convey value to the end-user. The second step is to establish a list of qualifying questions to be asked for each piece of equipment and utilities to facilitate the process and identifying areas of risk. Questions can include:

- Does the operator have to be a licensed technician?
- Do I need to program cycles at the start of operation?
- Do I have in-house start-up expertise?
- Is the equipment complex and difficult to operate – will I need operator training?

From here, those systems that present the greatest challenges and concerns should be considered for external, vendor support.

A secondary form of start-up procedures can be derived internally, but must fully account for the functionality and safety of the equipment or system.

Release of equipment upon successful completion of start-up verification. This suggests safety first. All equipment and utilities must function in a safe manner ensuring the protection of the operators.

Verification that design requirements have been satisfied. Verification of design requirements can be accomplished through several mechanisms throughout a project's lifecycle. To remain within the commissioning umbrella, design requirements can be incorporated into the commissioning procedures and verified as applicable. However, regardless of the methodology employed, the bottom line is that the design requirements must be satisfactorily met, verified, and documented.

Regardless of the definition, it is critical to ensure the commissioning definition is consistent with existing internal processes and practices. As with the ISPE Commissioning definition, the fundamental principles driving commissioning definition should be evaluated, re-designed, and implemented based on the level of applicability.

A Commissioning Compass

Having a sense of direction isn't the only benefit of carrying a compass; a compass establishes strategic alignment and presents a full-sphere approach to the upcoming tasks. If the commissioning compass is divided into four directions, it would look like - *Figure 3.*

Paving the path to success continues through the evaluation of scope and the critical activities that either fall under the commissioning umbrella or activities that impact the end-results of commissioning. Because the definition of commissioning can be

ID	Task Name	Duratio	Start	Finish	Pred	Resource Names
1	**Commissioning Activities**	**20.5 da**	**Mon 1/2**	**Mon 2/2**		
2	**Autoclave**	**20.5 da**	**Mon 1/2**	**Mon 2/2**		
3	Reciept Verification	0.5 da	Mon 1/2	Mon 1/2		Construction Manager
4	Equipment Install	5 da	Mon 1/2	Mon 1/3	3	Construction Manager
5	Instrumentation Calibration	2 da	Mon 1/3	Wed 2/	4	Metrology
6	Vendor Start-up	3 da	Wed 2/	Mon 2/	5	Vendor
7	Generation & Approval of CP	10 da	Mon 1/2	Mon 2/	3	Commissioning Team[50%],VAL[10%],ENG
8	Execute CP	5 da	Mon 2/	Mon 2/1	6,7	Commissioning Team[75%]
9	Generation & Aproval CP Sum	5 da	Mon 2/1	Mon 2/2	8	Commissioning Team[50%],VAL[10%],ENG

Table A. Project schedule.

broad, the activities involved in commissioning expand into FAT ending with the summary report for a commissioning procedure.

Figure 4 is a diagram of those activities leading up to and impacting the qualification phase.

Once the commissioning activities have been identified, a project team can then evaluate inter-relationships shaping the back-bone of the project schedule and areas where commissioning can be leveraged to support qualification. Beginning with the evaluation of interrelated activities, this exercise serves two primary functions facilitating project planning. First, understanding the how activities relate to one another sets the groundwork for project schedule predecessors and successors. This relationship essentially becomes the framework and template for a project schedule - *Table A.*

Secondly, the details of the assessment solidify the ability to leverage activities supporting qualification requirements and perform a total evaluation of the commissioning effort. Various illustrations and management tools can be designed highlighting the project strategy and project approach during this review as a thorough appraisal of the advantages and disadvantages of leveraging will be weighed - *Table B.*

Things to consider include:

- More time and resources needed earlier than later
- How are changes to systems captured and documented during commissioning? Would this be a formalized Change Control Program – possibly more stress and less flexibility during commissioning.
- Can we initiate IQ and commissioning concurrently? How will the installation changes be documented in the IQ protocol?
- Detailed vs. light commissioning documentation
- Quality Assurance (QA) responsibilities increase when leveraging commissioning.
- What happens when there are multiple failures or design issues when trying to leverage a specific test?
- Is commissioning truly serving the purpose of de-bugging the system? By leveraging commissioning activities and placing more emphasis on GDPs and GEPs, is validation then the safety net to complete unfinished commissioning/start-up activities?

At the conclusion of this effort, many critical decisions pertaining to the foundation of the commissioning program and the commissioning scope have been addressed and hopefully, several communication tools have been implemented ensuring the governing principles are transparent to key players.

Planning

By this phase, the definition of commissioning, the scope, a schedule backbone, and some project details have been addressed. The idea is to deliberately begin the process with the big-picture working through the specifics gradually and finalizing the specifics during the planning phase. This phase emphasizes two critical project tools: a commissioning plan and a project schedule.

The Commissioning Master Plan (CMP) derives from the more traditional document, a Validation Master Plan (VMP). Like a VMP, the CMP formalizes the commissioning program,

Filler	FAT	COM	IQ	OQ	PQ	Comments
Documentation Review			x			
As-built Drawing Verification			x			
Equipment Verification			x			
Instrument & Calibration Verification			x			This section should include the sensors
Utilities Verification			x			
Software Verification			x			Copy of ladder logics, back-ups, revision, etc
Hardware Verification			x			PLC, slots, racks, etc
Start-up/Shut-down Verification				x		
Fill Weigh/Partial Stopper Verification	x	x		x		During CP, confirm fill acuracy for 30 minutes, OQ fill accuracy for 120 min
Full Stopper Insertion Verification	x	x				
Fill Weight Range Verification	x	x		x		For Information Only
Reject Station Verification				x		
Alarm/Interlock Verification	x	x		x		Verification of sensors & e-stop
Power Failure Verification				x		As-found status
Screen Navigation				x		
User Access Verification				x		
Security Level Verification				x		
I/O Verification				x		

Table B. Testing matrix.

provides clear definitions, and creates a sense of fluency. This document also serves as a project training tool and is a constant point of reference for decision-making as the core elements of the document include:

- **Introduction:** provides an overview of the commissioning project.
- **Scope:** defines the limits of the document and commissioning activities.
- **Responsibilities:** identifies key functional areas and core responsibilities.
- **Commissioning Program**: defines the commissioning activities, the inter-relationships, the expected outcome of those activities, and the total project impact; this section also may address the generation, execution, and reporting of commissioning procedures.
- **Commissioning Support Programs:** defines the required support programs to be in place to successfully execute the plan; support programs can include change control, ETOP management, rolling completion list and punchlist management, and safety training.

The level of detail required for designing and executing a CMP varies across the board. If the document is intended to provide general guidance, place emphasis on existing polices, procedures, and programs currently employed, definitions functioning as a decision-making tool, and provide a general flowchart of expected activities and outcomes. Conversely, if the level of detail is substantially greater, consider including an impact assessment, specific testing requirements and acceptance criteria, and a project schedule.

The project schedule, the second critical project tool, is undoubtedly linked to the CMP and promotes strategic planning and project analysis. When designing the schedule, all aspects of the project should be considered from equipment delivery dates to preparing summary reports. The

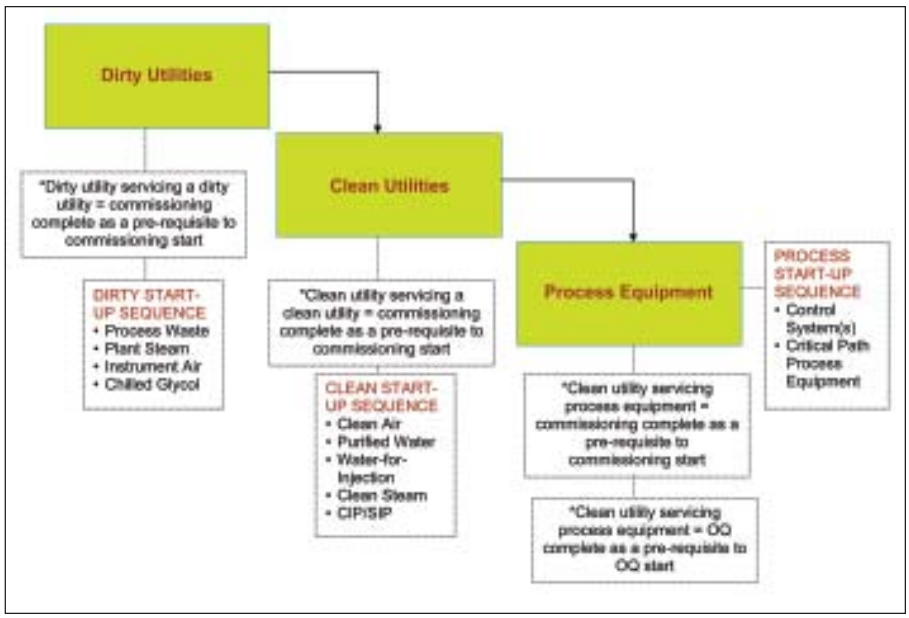

Figure 5. Commissioning process flow.

breadth of activities identified in the schedule creates functionality as each date reacts to changes in the timeline; this allows the end-users to fully understand the impact of slipping or changing milestones.

More importantly when compiling the schedule, it becomes vital to the project and the schedule to assemble a flow-chart indicative of system relationships and activity prerequisites - *Figure 5.*

By purposefully categorizing systems followed by a distinguished system list, key players can assess the utility requirements for successfully starting up the facility. As depicted in Table 6, all systems can be classified and placed under a single category. Only then, with all the systems in place, can a team determine utility service requirements and project links, such as a commissioning complete to commissioning start link.

With a solid foundation, it becomes appropriate to challenge and question additional project logistics. The earlier issues are put on the radar screen, resources can be identified and plans can be drafted in an effort to avoid chaos during a chaotic time as construction cycles through to completion. Other points to consider when planning include:

- What type of testing is required to release the utility systems?
- How does the control system fit into the picture –when is it needed, should this be a priority?
- Is there a difference in testing scope for qualified and non-qualified utilities?
- What role does the FAT and SAT play in commissioning?
- Identify system owners.
- What types of lists are needed – equipment, valves, instrumentation – what information will we need? Can our vendors adopt our numbering system to avoid re-tagging in the field?
- Seek to leverage existing procedures and policies for system-specific activities.
- What deems a system mechanically complete?
- When do you accept the system – what are the contractual terms?
- How will you coordinate the effort if construction is concurrent with commissioning?
- Who is responsible for safety issues such as Lock-Out Tag Out?
- Who issues and maintains the valve and instrumentation lists – who is performing calibration?
- What will the daily Commissioning Team meetings look like – what is the structure, content, time, and scope restrictions?

This type of systematic planning combined with a high-level, manageable schedule establishes a recipe for real-time updates and a fundamental understanding of how the facility can be started and commissioned in a safe, time-efficient fashion.

Procedure

The last preparation phase is generating the Commissioning Procedures (CPs) aligned with the project requirements. There are typically two formats for CPs; the first is a glorified checklist ensuring installation, functionality, and safety, and the second is a more formalized document with testing procedures and acceptance criteria - *Figure 6*.

When determining the format, consider the following:

- Blending the glorified checklist with the detailed approach and include a QA review creating the flexibility to leverage specific tests while minimizing the effort.
- Perform a GAP Analysis on the Vendor SAT and leverage that testing; prepare any additional tests to satisfy the commissioning requirements.
- Re-visit the difference between a Qualified system and a Non-Qualified system commissioning procedure – the requirements may be very different.
- Evaluate the flow of documentation as many resources have limited time for document review – this may mean weekly review meetings or the managed release of documentation, limiting the documents issued per week.
- Does your procedure synchronize with the CMP and existing project expectations?

COMPANY NAME **Project Title**

Engr. Spec. # System Equipment # P&ID #	Manufacturer Model # Serial #

Commissioning Activity	As-Found Status	Verified By Initial / Date
Pre-Requisites		
System is Mechanically Complete		
System start-up is complete		
As-built Drawings are available.		
System is tagged.		
Installation Verification		
System is level.		
System is clean internally & externally.		
Seals, gaskets, miscellaneous components are properly installed.		
Pressure safety devices are set to design requirements		
Operational Verification		
Jacket Temperature Test @ 25C		
Jacket Temperature Test @45C		
Agitation as designed (directions)		
Pressure Hold Test @ 80PSI		
Vacuum Leak Test		
Steam Test		
Water Transfer Verification		
Comments		

Reviewed By: (Commissioning Lead)	Date:
Reviewed By: (Engineering Lead)	Date:

Figure 6. Commissioning procedure example.

Regardless of the format, it is recommended to utilize a template as the benefits are plentiful. Realizing the paybacks of the template include building alliances with key players on wording and structure, minimized review time, limited formatting comments that may be time-consuming to resolve as they are centered on preferences, and streamlining the CP generation effort.

Points to Consider

As history will tell, many untapped issues will continuously surface throughout the project lifecycle; water samples will fail, system modifications will be made, gaskets will be replaced, and the facility will persistently evolve. While many issues will remain unknown and managed on a day-to-day basis, a commissioning team should consider project activities within their reach. Examine the following frequently asked questions:

Master Valve and Instrumentation List (V&IL)

- Does the Master V&IL capture both on and off skid components?
- Who owns the Master V&IL?
- Assign tag numbers based on internal numbering procedures; can an equipment vendor change tags prior to shipment or is this part of the construction management scope? When will tags be updated and how will this impact the generation of Installation Qualification (IQ) protocols?
- Did the vendors provide an electronic copy of system-specific V&ILs?

Calibration

- How are instruments classified, critical and non-critical, and where is criticality documented?
- Did the vendor provide a 'critical instrumentation list' identifying calibration ranges and requirements?
- At what stage of the project is calibration required – commissioning – qualification?
- Where and how will calibration be monitored? Who will be responsible

for re-calibration?

Turnover Packages

- Do you need a TOP matrix identifying requirements or is vendor package acceptable without any additional documentation?
- Would you prefer a standardized format for the TOPs? If yes, who is the resource responsible for compilation or is it part of vendor's scope?
- When will TOPs be available for protocol generation? Do the TOPs need to be 100% complete to begin protocol generation?

System Turnover (full ownership of a system)

- When is a system deemed mechanically complete?
- Is a final as-built drawing required prior to system turnover?
- What documentation is required for accepting a system?

Closing Thoughts

Commissioning is a dynamic effort accounting for many activities and requires extraordinary project management. At the heart of the effort is planning, more planning, and a little more. The power of planning early is frequently overlooked and underestimated. By systematically approaching the endeavor based on common goals, a team can collaboratively examine, explore, and implement project management tools designed for success. This common foundation is what carries a team, creates a sense of focus, and allows celebration for small victories. However, the greatest victory of all is actually completing the project—on time.

References

1. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 1 - Bulk Pharmaceutical Chemicals,* International Society for Pharmaceutical Engineering (ISPE), First Edition, June 1996, www.ispe.org.
2. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.

About the Author

Katie Henchir specializes in commissioning and qualification initiatives for the pharma/biotech industry. Henchir has worked on project teams throughout New England consistently delivering positive results. She holds a BS from Utica College, New York and a MBA from the Simmons School of Management, Boston, Massachusetts.

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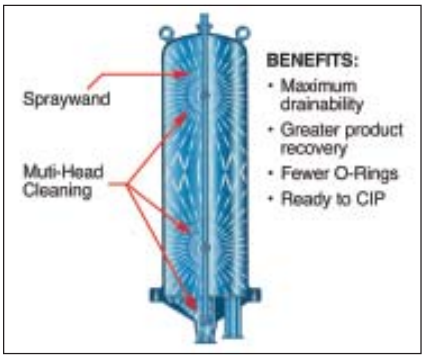
Equipment Identification and Lifecycle Analysis System

AdvantaPure has announced the availability of Process Equipment Tracking (PET), an equipment identification and lifecycle analysis system. PET is designed to identify and track process equipment such as pumps, hoses, biobags, diaphragm valves, filters, and UV lamps. Using radio frequency identification (RFID) technology, PET assists with the monitoring of equipment. Usage and cleaning cycles can be tracked to ensure timely maintenance and replacement before parts begin to fail, risk product integrity, and waste time and labor. **INTERPHEX Booth #1637**

AdvantaPure, 145 James Way, Southampton, PA 18966. www.advantapure.com.

Filter Housing



Allegheny Bradford Corp. has received a patent by the US Patent Office for its proprietary Opti-Clean style filter housing. Opti-Clean is the first and only multi-round filter housing designed for maximum drainability. Its technology eliminates the collection chamber of traditional housings and incorporates the cartridge plate right in the base. Each cartridge socket in the unique Opti-Clean is individually machined directly to the outlet port.

Allegheny Bradford Corp., PO Box 200, Bradford, PA 16701.www.abccorporate.com.

UV Water Treatment Product Series

Aquafine Corp. has introduced ChloRid, a series of proprietary UV water treatment products that eliminate residual chlorine/chloramine in applications such as pharmaceutical manufacturing and kidney dialysis. Aquafine's continued research supports these products as a popular method of chlorine/chloramine reduction utilizing UV technology. With Aquafine's findings, an improved understanding of chlorine/chloramines reduction chemistry enables reliable and economical sizing of reactors for pharmaceutical and dialysis applications. The results of Aquafine's research have been published and will be presented at INTERPHEX 2006. **INTERPHEX Booth #2505**

Aquafine Corp., 29010 Avenue Paine, Valencia, CA 91355. www.aquafineuv.com.

Liquid Delivery Measurement and Quality Assurance System

ARTEL has announced the MVS 2.0, which verifies liquid delivery quality assurance at extremely low volumes and with non-aqueous test solutions, such as DMSO. With the MVS 2.0, laboratories can now verify the performance of multichannel liquid handlers with up to 384 pipette tips. Using photometric calibration for enhanced accuracy and precision, the MVS 2.0 provides an internationally approved method for ensuring data integrity at the low volumes characteristic of 384-well plates. The MVS 2.0 will also allow users to test with reagents of various viscosities so that calibration procedures are identical to actual assay conditions.

Artel, 25 Bradley Dr., Westbrook, ME 04092. www.artel-usa.com.

Packaging Solutions

Bilcare develops custom and commercial packaging solutions that address brand identity, counterfeiting, total effective cost, manufacturing efficiency, shelf life and global distribution. Bilcare's metallic luster mono/multi layered barrier films, patina™, ultra™, ultra tx™, impart a high level of physical, functional and counterfeit protection as well as enhanced brand identity. Bilcare's nova™ calendared paper lidding is available in various color combinations with PVC film for brand identity, anti-counterfeiting and cost efficiency. With a focus on helping the customer select the best packaging materials available for their product, Bilcare takes a start-to-finish approach to a product to enhance its value from development through commercialization. **INTERPHEX Booth #P2178**

Bilcare, Inc., 300 Kimberton Rd., Phoenixville, PA 19460. www.bilcare.com.

Decontamination and Aseptic Transfer Systems

Bioquell Inc.'s Clarus® equipment effectively kills microorganisms while avoiding material compatibility issues. Bioquell's patented process of hydrogen peroxide vapor generation is routinely used for research and manufacturing facilities including fermentation/ purification suites. Bioquell's Clarus Port is designed and configured to suit all major small-scale aseptic processing needs. Although the chamber and unit size is standard, there are three interface configurations for rigid wall, flexible canopy and "dockable" applications. **INTERPHEX Booth #785**

Bioquell Inc., 101 Witmer Rd., Suite 400, Horsham, PA 19044. www.bioquell.com.

Centrifuge with Direct Contact Drying

Bolz-Summix offers a centrifuge which incorporates inverting basket technology for separation/filtration and direct contact drying of the material to provide tremendous processing advantages. With this combination of technologies, it is possible to select the exact final moisture content of the finished product. Other advantages include no residual heal remains on the filter cloth, homogenous cake build-up, no compression of the solids cake, and full flexible process recipe management. **INTERPHEX Booth #A2636**

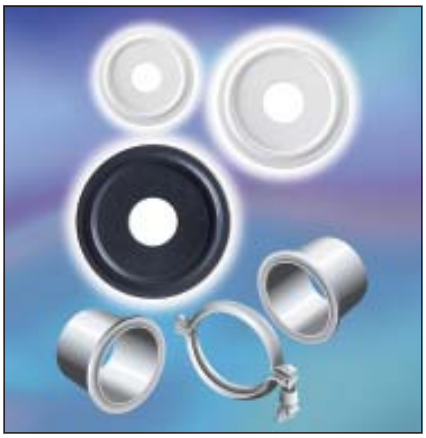
Bolz-Summix, 520 Sharptown Rd., Swedesboro, NJ 08085. www.bolz-summix.com.

Biowaste System

Budzar Industries, Inc. designed the Continuous Biowaste Inactivation (CEI™) system for use in research, production and bio-containment environments. The Biowaste system consists of three zones: holding tank, waste deactivation, and cooling. Options are available for seal less pumps, PLC control and monitoring, and PH control before discharging. **INTERPHEX Booth #1060**

Budzar Industries, 38241 Willoughby Pkwy., Willoughby, OH 44094. www.budzar.com.

Seal Solution



The Busak+Shamban Isolast® plus Sanitary Pipe Flange Gasket offers a sealing solution exclusively designed and formulated for quick connectors in pipe work for pharmaceutical, medical, and biotechnology processing systems. Busak+Shamban's proprietary Isolast® perfluoroelastomer (FFKM) offers exceptional chemical and thermal resistance without sacrificing the essential performance of elastomers. Busak+Shamban offers an extensive product line with more than 2,000 material compounds available to produce seals and bearings for static, dynamic, reciprocating, or rotary applications. **INTERPHEX Booth #1824**

Busak+Shamban Americas, 2531 Bremer Rd., Fort Wayne, IN 46803. www.busakshamban.us.

High-Speed Centrifuge

The Celeros Model APD is a high-speed centrifuge that achieves solids recovery and centrate clarity. This precision solids handling centrifuge uses a novel, automated piston to discharge sedimented materials from the centrifuge bowl as a dry-paste, which can be easily transferred or reconstituted for further processing. Combining low shear flow-path features and rotational speeds from 0-20,000 x G, the multi-purpose APD centrifuge is designed to address the needs of laboratory scales through industrial separation process applications (10-10,000 liter volumes). Celeros APD centrifuges are suitable for cell harvesting and debris removal, blood plasma fractionation, vaccine manufacturing, and microbial processing. **INTERPHEX Booth #483B**

Celeros, Inc., 40000 Grand River,

Suite 406, Novi, MI 48375. www.celeros-separations.co.

Sterilization System

ClorDiSys Solutions, Inc., is introducing the expanded volume Minidox-M chlorine dioxide gas sterilization system. The unit provides a rapid and highly effective method to decontaminate rooms, isolators, and processing equipment up to 60,000 cubic feet without adjustments or additional equipment. The Minidox-M offers a sophisticated, fully integrated, sterilant concentration monitoring system, which provides precise monitoring and control of gas concentration. By using a true gas, the system benefits include a more efficacious cycle due to better distribution into hard to reach areas and quicker aeration. **INTERPHEX Booth #2609**

ClorDiSys Solutions, Inc., PO Box 549, Lebanon, NJ 08833. www.clordisys.com.

Packaging System

Dividella, a division of Koerber Medipak NA, has introduced the NeoTOP 104, a semi-automatic packaging machine that forms and erects NeoTOP cartons, including integrated partition from flat blanks. Cylindrical objects, applicators, tubes, medical devices or blisters are then laid in manually. At the closing station the packs are tucked in and sealed by gluing station. The machine is designed for applications where flexibility for small lots or clinical trials is required. **INTERPHEX Booth #P2005**

Dividella AG, Werdenstrasse 76, 9472 Grabs, Switzerland. www.dividella.com.

Hygienic Meter

Emerson Process Management has extended its selection of the Micro Motion® H-Series line by offering the 15 Ra electro-polished surface finish on its 2-inch line size hygienic Coriolis meter. This new addition expands the H-Series line by offering all five line sizes with the electro-polished finish. For customers needing high-performance flow measurement in hygienic applications, this new Micro Motion Coriolis meter offers customers the ideal solution for applications in need of excellent accuracy and reliability, as required in biotech, pharmaceutical, food and beverage applications, and for the measurement of ultra-pure gas. **INTERPHEX Booth #A1837**

Emerson Process Management PO Box 4100, 8000 W. Florissant Ave., St. Louis, MO 63136. www.emersonprocess.com.

Metal Detector

Eriez' highly sensitive E-Z Tec® Pharmaceutical Metal Detector improves process purity through detection of minute metal contaminants during the production of any capsule or tablet-based product. The unit's advanced electronic design simplifies setup, ensures reliable operation, provides instantaneous recovery from phase adjustments and requires minimal operator training. E-Z Tec Pharmaceuticals are designed to fit most any production line configuration. A new 5-minute QuickStart feature allows users to pass sample product, test and begin production in less than five minutes. **INTERPHEX Booth #A2129**

Eriez, 2200 Asbury Rd., Erie, PA 16506. www.eriez.com.

Controller and Indicator

Eurotherm, a unit of Invensys plc, has introduced the 1/8 DIN controller and indicator with text display, model 32H8, the latest addition to their 3000 series temperature/process controllers. The

32H8 has a text display, high accuracy input, 5 on-board process recipes, as well as Eurotherm's patented "Instant Accuracy®" system. Scrolling alarm and event messages are unique features that can alert an operator of a change in plant conditions. These messages can be customized with a PC tool, thereby providing terms and expressions familiar to the operator.

Eurotherm, 741-F Miller Dr., Leesburg, VA 20175. www.eurotherm.com.

Dust Collector

The Gold Series® Camtain ™ Dust Collector from Farr Air Pollution Control provides safe-change containment of hazardous dusts in pharmaceutical manufacturing environments. It is the first in the dust collection industry to use a bag-in/bag-out access door and dust discharge system that have been fully surrogate-tested to ensure optimum protection of employees and indoor environments. The collector uses HemiPleat ™ filter cartridges with a patent-pending, open pleat media that results in greatly extended service life and lower pressure drop compared to standard cartridges – typically double the life at half the delta P. Rated filter efficiency is 99.999 percent on 0.5 micron particles and larger. **INTERPHEX Booth #3446-8**

Farr Air Pollution Control, 3505 S. Airport Rd., Jonesboro, AR 72401. www.farrapc.com.

Cell Density Sensor

Finesse, LLC has announced the introduction of the TruCell – Cell Density Sensor for bioprocess applications. The unique features of this product include its 12mm design as well as its use of Laser technology instead of older LED technology. The TruCell – Cell Density Sensor uses digital technology for operator interface and communication of the measured values. Therein, the TruCell is available as either a Bluetooth or Foundation fieldus enabled device. **INTERPHEX Booth #A2431**

Finesse, LLC, 3230 Scott Blvd., Santa Clara, CA 95054. www.finesse-inc.com.

Automated Permeability Measurement

Freeman Technology will introduce a Permeability Module for the company's FT4 Powder Rheometer. The FT4 Powder Rheometer is a fully automated universal powder tester for the comprehensive characterization of powder flowability. The Permeability Module uses a pressure transducer to measure pressure drop across the height of a powder bed in the system's test vessel while the air velocity through the powder is controlled. Conditioning of the sample before evaluation ensures a homogeneous, stress-free and reproducible packing condition. **INTERPHEX Booth #P2335**

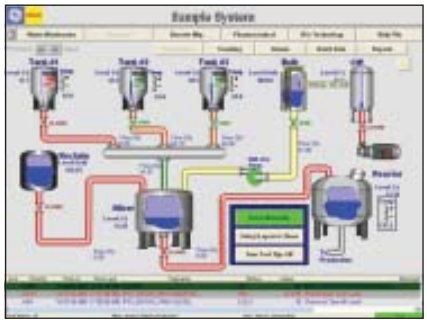
Freeman Technology, Boulters Farm Centre, Castlemorton Common, Welland, Worcestershire WR13 6LE, United Kingdom. www.freemantech.co.uk.

On-line TOC Analyzer

GE Analytical Instruments, a division of GE Water and Process Technologies, has introduced the Sievers 500 RL On-Line TOC Analyzer. The highly automated Sievers 500 RL was designed to deliver science-based risk management capability to the production floor for Process Analytical Technology (PAT) and other quality initiatives such as real-time pharmaceutical water release and on-line cleaning validation. The reagentless Analyzer incorporates features such as the Super iOS that automate high-risk and frequently performed activities, significantly reducing labor costs and eliminating the delays associated with laboratory analyses. The Sievers Super iOS standards introduction device fully automates the delivery of multiple standards. **INTERPHEX Booth #1809**

GE Analytical Instruments Div., 6060 Spine Rd., Boulder, CO 80301. www.geinstruments.com.

Automation Software Platform



GE Fanuc Automation, Inc., a unit of GE Industrial, has announced the availability of Proficy HMI/SCADA - iFIX 4.0, an industry solution for the comprehensive monitoring, control and distribution of plant-wide data. A key component of the Proficy™ automation software platform, this new release of iFIX 4.0 delivers enhanced functionality including third-party PLC integration, productivity enhancements and the ability to handle one of the world's largest SCADA systems, the Changi Water Reclamation Plant in Singapore. The SCADA system will process approximately 500,000 tags across an architecture of 50 nodes and will be running the Proficy iFIX 4.0. **INTERPHEX Booth #1809**

GE Fanuc Automation, PO Box 8106, Charlottesville, VA 22906. www.gefanuc.com.

Combination Centrifuge – Dryer

Heinkel's TZT combination centrifuge – dryer combines the two key process steps of contained filtration/separation via centrifuging and contained drying within a single machine. It reduces batch cycle times from 40%-50% over conventional two machine processing. This system offers the high productivity and washing efficiency of a filtering centrifuge with forced convection and fluidized bed drying. The Heinkel TZT is ideal for highly active compounds, pharmaceutical API's and Intermediates, or hazardous materials where traditional two stage filtration and drying equipment processing could result in containment difficulties during the transfer of materials from one machine to another. **INTERPHEX Booth #A2636**

Heinkel USA, 520 Sharptown Rd., Swedesboro, NJ 08085. www.heinkel.com.

Powder Screeners

HK Technologies, a subsidiary of The Cleveland Vibrator Company, will showcase its powder screeners at INTERPHEX 2006. The high-energy vibratory Dr. is totally enclosed in brushed 316 stainless steel. The unique over/center motor mount, coupled with their quadweight system allows the operator to adjust the amount of screen shear while providing maximum product throughput. HK Technologies, Inc. utilizes a combination of mechanical vibration coupled with ultrasonics to produce a vibratory system that significantly reduces or eliminates screen blinding in many powder applications. **INTERPHEX Booth #2716**

HK Technologies, 2828 Clinton Ave., Cleveland, OH 44113. www.clevelandvibrator.com.

Enclosures

Hoffman has introduced PharmaPro™, a standard series of Stainless Steel Type 4X Flush-mount Enclosures. The models feature a low Roughness Average value PharmaPro™ Finish that minimizes surface crevices, allowing a more thorough wipe-down. Designed for wall mounting, these enclosures also minimize exposed surfaces where dust, bacteria and other undesirable contaminants can accumulate. Constructed of 304 and 316 stainless steel, the PharmaPro Flush-mount Enclosure is suitable for stud and block wall installation and held securely by a patent pending in-wall mounting system. **INTERPHEX Booth #A2237**

Hoffman, 2100 Hoffman Way, Anoka, MN 55303. www.hoffmanonline. com.

Powder Transfer Processing

ILC Dover will introduce the G2Pac, the Smart FIBC, the next generation technology for cGMP powder transfer operations. Improved processing and direct operational cost savings result

from reductions in product loss, cross contamination, cleaning, cleaning validation, and water/solid waste disposal. **INTERPHEX Booth #2522**

ILC Dover, One Moonwalker Rd., Frederica, DE 19946. www.ilcdover.com.

Flooring System

Key Resin Company offers Key Epoxy Terrazzo, a resinous flooring system that combines the highly decorative appearance of marble with durability, chemical resistance and ease of maintenance. Applications of Key Epoxy Terrazzo are ideal for medical manufacturing facilities with high traffic such as laboratories, hospitals, pharmaceutical plants, and even cafeterias or lobbies. The product does not support bacterial growth and is also available in conductive and novolac formulations. The flooring system exhibits excellent resistance to pin-holing and drain out. **INTERPHEX Booth #3156**

Key Resin Company, 4061 Clough Woods Dr., Batavia, OH 45103. www.keyresin.com.

Particle Size Analyzer

Malvern Instruments will show the Insitec Pharma Voyager on-line/automated at-line particle size analyzer. Launched at last year's INTERPHEX event, this mobile system is proving to be an attractive option in pharmaceutical manufacturing, especially for pilot plant operation and PAT research, where mobility, cleanability and ease of operation are important. A completely mobile and self-contained unit, Pharma Voyager delivers on-line continuous or automated at-line particle size measurement for solid particulates suspended in gas streams. It provides real-time size analysis of particles in the size range 0.5 to 1000 microns, and features CIP, SIP and 21CFR compliance, and validation with material certificates. **INTERPHEX Booth #1040**

Malvern Instruments Ltd., Enigma Business Park, Grovewood Rd., Malvern, Worcestershire WR14 1XZ, United Kingdom. www.malverninstruments.com.

Permanent Valve and Instrument Tags

Marking Services, Inc. offers Type 316 stainless steel tags that have permanent Laser-Engraved text that is clearly readable and can only be removed with a hand grinder. They're designed to survive the harshest plant environments and exposure to higher operating temperatures. Marking Services also offers MS-215 tags with all printing between layers of chemical-resistant plastic to withstand repeated contact with repeated washdowns and all process chemicals in cleanroom and cGMP environments. Both types of tags can be affixed with tough 7 x 7 braided type 316 wire and crimps to eliminate missing tag problems. **INTERPHEX Booth #867**

Marking Services, Inc., 8265 N. Faulkner Rd., Milwaukee, WI 53224. www.markserv.com.

Live Wireless Validation and Monitoring System

Masy Systems, Inc. will demonstrate the rl2000 Live Wireless Validation and Monitoring System at INTERPHEX 2006. The rl2000 Live Wireless System is a solution for pharmaceutical and biotech validation and monitoring applications where hardwired systems are not practical or cost effective, such as warehouses, environmental chambers, clean rooms and laboratories. The rl2000 System, comprised of portable hand-held transmitters and PC-interfacing receivers, offers many benefits for pharmaceutical and biotech validation and environmental monitoring when compared to traditional hardwired data acquisition technologies. Unlike other wireless products that are "blind" data collectors, the rl2000 enables "live" viewing of data, trends and alarms during validation and environmental monitoring. **INTERPHEX Booth #C114**

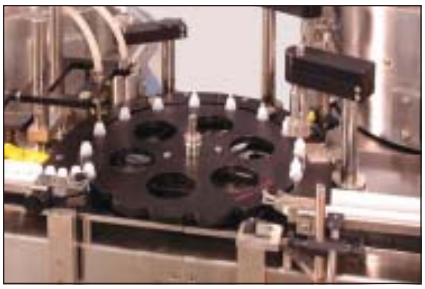
Masy Systems, Inc., PO Box 485, Pepperell, MA 01463. www.masy.com.

Biopharmaceutical Filtration and Separation Product Catalog CD

Millipore Corp. has announced that its multi-language 2006 Biopharmaceutical Filtration and Separation Product Catalog on CD is now available. Including English, French, Spanish, German and Italian this electronic catalog contains detailed product information for Millipore's filtration, chromatography and disposable manufacturing solutions. Designed for ease of use this tool provides easy navigation by application, process step or product name, as well as text and catalogue number search capability. Millipore's Bioprocess division delivers integrated solutions and services for every application, every step and every scale of the drug development and manufacturing process. **INTERPHEX Booth #2221**

Millipore Corp., 290 Concord Rd., Billerica, MA 01821. www.millipore.com.

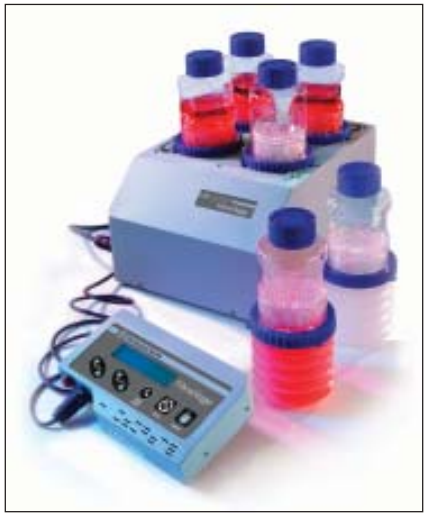
Filling System



National Instrument's Filamatic® will feature its newest engineering design for the Mini-Monobloc Filling System at INTERPHEX 2006. The Mini-Monobloc is specially designed for servomotor filling, stopper placement and crimp sealing of two sizes of glass vials. This single index system is designed to operate at a rate of 30 machine cycles/minute and includes all necessary change parts to accommodate two sizes of vials, four styles of stoppers and two sizes of crimp seals. Ideal for pharmaceutical, diagnostic and biotech pilot plants or for limited space requirements, the Mini-Monobloc's compact size, efficient operation and portability enable this unit to be moved easily and relocated as required. **INTERPHEX Booth #A1848**

National Instrument Co., Inc., 4119 Fordleigh Rd., Baltimore, MD 21215. www.filamatic.com

Disposable Cell Culture System



New Brunswick Scientific will showcase its FibraStage™ system at INTERPHEX 2006. The disposable cell culture system reduces operating cost and labor, producing high yields of protein, virus or cell mass from anchorage-dependent or suspension cultures. The system is comprised of 500 mL disposable bottles, pre-filled with FibraCel® disks – a unique solid-support matrix for producing high-density cultures. Cells growing in, on, or between the porous, multi-layer disks are provided with a shear-free environment and extremely high-surface area for cell growth. **INTERPHEX Booth #962**

New Brunswick Scientific, 44 Talmadge Rd., Edison, NJ 08818. www.nbsc.com.

Leak Detector

Nikka Densok will display the HDV-AT6 Pinhole Inspector for the inspection of glass vials ranging from 2ml to 50ml in size at speeds up to 24,000 vials per hour. The Nikka Densok High Voltage Method of inspection coupled with the ACE-trak® material handling system developed by Diamond Machine Werks, allows complete vial body inspection of a wide range of vial sizes on one machine. The non-destructive inspection method allows defects such as cracks, pinholes and cap seal imperfections to be identified where not visually detectable. The ergonomic design enables ease of operation, maintenance and quick changeover time for all product sizes. **INTERPHEX Booth #P1882**

Nikka Densok USA, Inc., 610 Garrison St., Suite D, Lakewood, CO 80215. www.nikkadensok.com.

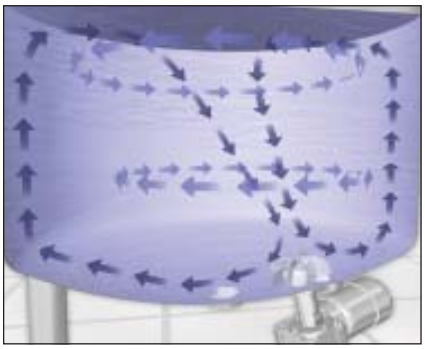
Deduster

The Kramer E3100 WIP is a washable vertical conveying deduster designed to be used in production situations with high potent products. The E3100 is 100% water and dust tight to significantly reduce operator exposure levels. To accommodate various water supplies for washing, the Kramer E3100 WIP is available in three different wash cycles; Flooding, Wash-Down and Sequential wash. In addition, this unit can be used as a stand-alone or can be integrated as a combination unit with a washable Lock metal check. **INTERPHEX Booth #2822**

Pharmaceutical Machine Supply, LLC, 901 Bridgeport Ave., Building

#8-B, Shelton, CT 06484. www.pms-usa.net.

Mixer



PremierTec will introduce the PremierTec Ultra Clean Mixer at INTERPHEX 2006. The Mixer is designed to improve the mixing of liquid products in pharmaceutical, biotech and chemical ultra clean processes. It is magnetically coupled through the bottom of the mixing vessel. Therefore, a seal through the vessel is not required to transmit coupling/power to the mixer. The design also maintains the original strength of the earth magnets, and due to this strength, the impeller actually "floats," with the male (stationary) bearing used only as a stabilizer/ guide bearing. **INTERPHEX Booth #A173**

PremierTec, 1100 Commerce Dr., Racine, WI 53406. www.premiertec.net.

Intelligent Reactor Systems

Powder Systems Ltd., has developed a series of intelligent reactor systems which allow any chemical or biological process to be monitored, controlled and optimized to help get products to market faster. Based upon patented COFLUX® technology, the reactors allow faster scale-up through to production. For the first time, accurate, usable calorimetric data can produce meaningful information during process development - a key parameter for any PAT initiative, as processes are scaled-up. These systems provide effective process analytics in the form of enthalpy, power, and heat transfer coefficient enabling a clear and accurate measure of the status and progress of any reaction. **INTERPHEX Booth #1049**

Powder Systems Ltd., Estuary Business Park, Liverpool L24 8RG, United Kingdom. www.powdersystems.com.

Male Lock Syringe

Qosina has added a medical-grade, black opaque male luer lock syringe (Part # 13134) to their inventory. The syringe is made from high-density, acid resistant polypropylene approved for medical applications. The syringe is excellent for use with UV or visible light curing and it can also dispense low viscosity materials and fissure sealants. The barrel/plunger assembly has a non-reactive silicone seal assuring material compatibility. **INTERPHEX Booth #568B**

Qosina, 150-Q Executive Dr., Edgewood, NY 11717. www.qosina.com.

Co-Extrusion Technology

Rommelag® has introduced their bottelpack® Co-Extrusion Blow/Fill/Seal technology. This aseptic filling technology allows customers to create a unique container by utilizing barrier materials in the container walls. Co-Extrusion technology containers can be designed with high barriers to permeation, specialized materials chosen for product compatibility, barriers to improve shelf life, and many other applications. Bottelpack® Co-Extruded container designs can eliminate the need for secondary packaging. **INTERPHEX Booth #1033**

Rommelag USA, Inc., 1090 King Georges Post Rd., Suite 507, Edison, NJ 08837. www.rommelag.com.

Airlock Sieve

Russell Finex has introduced the patent-pending Compact Airlock Sieve. Its validatable pneumatic clamping system gives large improvements in product containment and operator health and safety. With powders safely contained, the sieve accurately removes oversize contamination using the mesh

screen fitted to the unit, while the good product passes through the mesh and on to the next stage of production. The unit is clamped together with a pneumatic revolutionary airlock system. **INTERPHEX Booth #2722**

Russell Finex Inc., 625 Eagleton Downs Dr., Pineville, NC 28134. www.russellfinex.com.

GSK Partners with SDL to Speed Product Submissions

SDL International has received a contract worth over $525,000 for technology and consulting services from GlaxoSmithKline (GSK) to implement simultaneous multilingual product submissions to the European Medicines Agency (EMEA). GSK expects to see significant business advantages by reducing the time necessary to pass the EMEA regulatory process through the deployment of the SDL GIM solution. A key decision factor was SDL's ability to support and enhance the process of creating content compliant with EMEA's XML-based product information (PIM) standard and adapting the XML content to the European Union's 20 languages.

SDL International, Globe House, Clivemont Rd., Maidenhead, Berkshire SL6 7DY, United Kingdom. www.sdl.com.

Preparative Chromatography Devices

Seika Corp. of America is a provider of preparative chromatography devices for laboratory, pilot, and production scale use. Products include YMC chromatography media, HPLC and Biochromatography systems, and components (including pumping skids, injection systems, glass and stainless steel column devices, and various detectors) for purification of small molecule and biopharmaceutical products. Additionally, a full range of contract process development and manufacturing services are offered. **INTERPHEX Booth #485B**

Seika Corp. of America, 701 W. Broad St., Suite 204, Bethlehem, PA 18018. www.seikacorporation.com.

Sparta Systems Completes PDA Audit

Sparta Systems, Inc., maker of TrackWise®, the leading product for Quality Management Systems software for life science and other highly regulated industries, has announced that it has successfully completed its 3rd Parenteral Drug Association (PDA) Software Supplier Quality Audit. The Pharmaceutical Industry Software Supplier Quality Audit, conducted by SynTegra, an independent, PDA approved auditor, allows Sparta's customers to meet federal government auditing requirements for companies that supply software solutions to the pharmaceutical industry. Sparta Systems' completed audit report will be available at SynTegra's Audit Resource Center, which provides online access to a secure audit data repository.

Sparta Systems, Inc., Holmdel Corporate Plaza, 2137 Highway 35, Holmdel, NJ 07733. www.sparta-systems.com.

Stainless Steel Maintenance Hand Tools

Steritool will introduce an all stainless steel driver handle for their comprehensive line of stainless steel maintenance tools at INTERPHEX 2006. For maintaining sterility in the servicing of process equipment in a sterile environment, stainless steel hand tools are an efficient and cost effective solution. Stainless steel requires no plating, which can generate dangerous particulate, to maintain its corrosion resistance. In the event the surface is scratched or damaged, stainless steel forms a pure chromium oxide (a passive, non-reactive) layer, protecting it against further corrosion without exposing ferrous surfaces that can contaminate a Cleanroom environment. **INTERPHEX Booth #3165**

Steritool, 196 Wyckoff St., Brooklyn, NY 11217. www.steritool.com.

Qualification Micronizer

The Qualification Micronizer® jet mill from Sturtevant Inc. enables pharmaceutical laboratories to develop powder formulations with desired fine particle sizes on small scale, before confidently proceeding to clinical trial and production quantities. Designed for experimental batches of 5-20 grams, the versatile Qualification Micronizer® can mill up to half a pound of material per hour, yet is capable of feed rates as low as a few grams per hour with maximum sample recovery. The fines it produces have a narrow particle-size distribution, with particle diameters as small as a few microns. Other benefits include low air consumption, low operating noise, and no heat buildup. **INTERPHEX Booth #A1753**

Sturtevant Inc., 348 Circuit St., Hanover, MA 02339. www.sturtevantinc.com.

Serialized Product Tracking

Systech International has announced the introduction of its TIPS Serialized Product Tracking solution. Designed to combat counterfeit and diverted product challenges, the solution works in concert with RFID and bar code tech-

nologies. The solution enables complete mass serialization and track and trace of item-level products. TIPS Serialized Product Tracking is part of Systech's comprehensive suite of machine vision inspection, packaging line automation, and information management solutions. **INTERPHEX Booth #P1955**

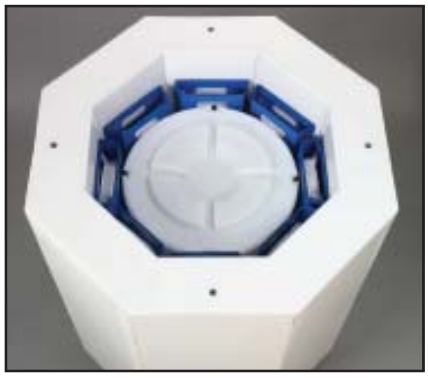
Systech International, 2540 Route 130, Suite 128, Cranbury, NJ 08512. www.systech-tips.com.

Ceramic Membranes

TAMI has developed a complete range of tubular membranes for many industrial applications where filtration/molecular separation processes are required. For industrial applications, the cross-flow operation is preferred because of the lower fouling tendency relative to the dead-end mode. TAMI ceramic membranes allow all operations of separation in the Microfiltration, Ultrafiltration and Fine UF range. TAMI ceramic membranes are environmentally friendly, and resistant to pressure, solvents, acids and bases, and high temperatures. **INTERPHEX Booth #1480**

TAMI North America, 2865 Sabourin Street, St-Laurent, Quebec H4S 1M9, Canada. www.tami-na.com.

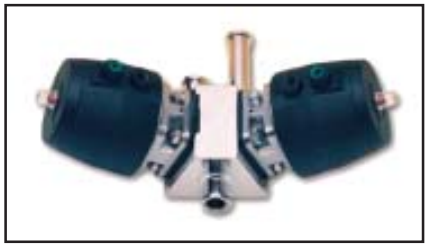
Bulk Shipping Container



ThermoSafe Brands has introduced the ThermoSafe® Durable Transport insulated bulk shipper. The bulk shipper is pre-qualified to keep bulk loads of liquid bio-substances at refrigerated temperatures for up to 96 hours. It is a unique, octagonal-shaped, pre-qualified shipping system designed to hold 2-8°C refrigerated temperatures for up to four days under extreme ambient temperatures. The reusable container can hold bulk drums of liquid from 35 to 100L capacities, or other capacities as needed. **INTERPHEX Booth #P2056**

ThermoSafe Brands, 3930 Ventura Dr., Suite 450, Arlington Heights, IL 60004. www.thermosafe.com.

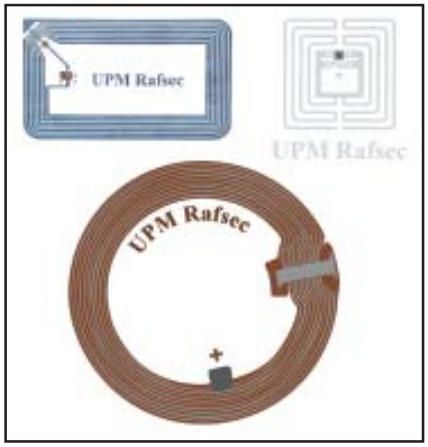
Valves



Top Line offers a line of multi-ported divert valves that are very popular in process applications where space considerations are critical. Top-Flo[å] Divert Valves are available in two-way, three-way, four-way, and five-way configurations and can be supplied with manual and actuated bonnets. This patented design eliminates deadlegs inherent in typical mixing or diverting applications. A wide variety of inlet and outlet tubing configurations and polish combinations are available.

Top Line Process Equipment Co., 21 Valley Hunt Dr., Lewis Run, PA 16738. www.toplineonline.com.

Radio Frequency Identification Tags and Inlays



UPM Raflatac's Rafsec products are being used in numerous Radio Frequency Identifcation (RFID) roll-outs and pilots worldwide including the Aegate pharmaceuticals tracking system. UPM Raflatac RFID business manufactures both HF and UHF passive tags and inlays in high-volumes. UPM Raflatac will showcase at INTERPHEX 2006, the Rafsec 45x76 mm and Rafsec 16x28 mm, Rafsec Round 25 mm, Rafsec 10x23 mm, and Rafsec G2 "Mini". These Rafsec HF and UHF products are available as tag, wet inlay, dry inlay and in-mold tag. **INTERPHEX Booth #E2659**

UPM Rafsec, PO Box 669, 33101 Tampere, Finland. www.rafsec.com.

Flat Panels and Workstations

VarTech Systems will showcase NEMA compliant flat panels and workstations at INTERPHEX 2006. Vartech Systems is a provider of aseptic industrial grade LCD flat panel display systems, fully enclosed computers, and rugged sealed workstations. The company's products offer NEMA 4 (IP65), NEMA 4X (IP66) or NEMA 6P (IP68) protection. Sizes supported range from a small form-factor 6.4" design up to an impressive 23.1". **INTERPHEX Booth #P1958**

VarTech Systems, Inc., 11529 Sun Belt Ct., Baton Rouge, LA 70809. www.vartechsystems.com.

Containment and Isolation Systems

Vector Corp. will display multiple lines of solid dosage processing systems at INTERPHEX 2006. The systems feature product containment and isolation enclosures for safety protection of the operator and the environment when processing potent materials. Vector provides containment and isolation systems for laboratory, pilot and production sizes of fluid bed granulators/coaters/dryers, tablet coaters, roller compactors and high shear granulators. Each system is specifically designed to meet the safety requirements established by customers based upon the safe exposure limits of the product(s) being processed. **INTERPHEX Booth #1455**

Vector Corp., 675 44th St., Marion, IA 52302. www.vectorcorporation.com.

Pump and Tubing Solutions

Watson-Marlow Bredel will showcase its biopharmaceutical processing solutions, including the 520Di- and 620Di-dispensing pumps and Pumpsil®, Pumpsil-D and Bioprene® tubing at INTERPHEX 2006. The 520/620 family of peristaltic pumps are designed for the accurate metering, dosing, and transferring of corrosive or sensitive fluids in sanitary environments. Pumpsil tubing is a platinum-cured silicon tubing designed with an ultra-smooth bore to control protein binding and bacterial growth. The Pumpsil-D is specifically formulated for high accuracy dispensing applications in the biopharmaceutical industry. New to this year's lineup is Watson-Marlow Bredel's Bioprene tubing, a Thermoplastic Elastomer (TPE) tubing which is an alternative to latex or silicone and ideal for biophar-maceutical applications. **INTERPHEX Booth #1405**

Watson-Marlow Bredel, 37 Upton Technology Park, Wilmington, MA 01887. www.watson-marlow.com.

Software for Clinical Trials Manufacturing

Werum Software and Systems has released PAS-X CT, the suite for Clinical Trials Supply, specifically designed to manage and coordinate the production of clinical trial supplies. PAS-X CT has been optimized to achieve three main objectives in the supply chain of Investigational Medicinal Products: providing ease of definition and high flexibility in the planning phase of clinical trials, achieving regulatory compliance during all phases of production, and assuring operational excellence in packaging and labelling operations. PAS-X CT provides all the functionality needed to manage clinical supply materials in an integrated manner, so that all parties are able to access the same information and are provided the visibility needed to be efficient collectively.

Werum Software and Systems, 44 Indian Ln. E., Towaco, NJ 07082. www.werum-america.com.

West Virginia as a Business Location

West Virginia lies in the heart of the Appalachian Highlands. The state offers countless choices for work, home and play, giving West Virginians the opportunity to create lifestyles uniquely their own. There are cost advantages to long-term investment in West Virginia due to the state's strategic location, expert work force, vast supply of natural resources, ready infrastructure and advanced technology. Profitability for the pharmaceutical and medical manufacturing industry in West Virginia is 5.6 percentage points higher in West Virginia than in the U.S. and labor costs are $2,561,177 lower. **INTERPHEX Booth #489**

West Virginia Development Office 1900 Kanawha Blvd. E., Charleston, WV 25305. www.wvdo.org.

Pulsed UV Sterilization System

Xenon Corp. has introduced the SteriPulse-XL Surface Decontamination System, a non-contact sterilization system that instantly kills microorganisms on the outside of packages, to prevent the contents from becoming contaminated when opened. The System employs pulsed UV light to sanitize the outside of packages containing sterile contents and prevents the introduction of microorganisms to a cleanroom or other sterile area. Capable of six log kill in under one second, this low temperature, non-contact system eliminates the need for vapors and toxic chemicals and can be integrated into most on-line isolation transfer ports. Featuring 16 inch lamps which deliver high peak energy 100,000 times more powerful than the sun, the System destroys the DNA repair mechanism of microbes.

Xenon Corp., 37 Upton Dr., Wilmington, MA 01887. www.xenoncorp.com.

*To submit material for publication in **Pharmaceutical Engineering**'s New Products and Literature department, e-mail press releases with photos to **pharmeng@ispe.org** for consideration.*

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Risk Management for Highly Hazardous Compound Manufacturing

by Rochelle Runas, ISPE Technical Writer

Can highly hazardous compounds, such as steroid hormones and cytotoxics, be processed safely in multi-product facilities? It is a controversial issue that a team of industry leaders have begun to tackle in hope of shifting away from the paradigm of separate production facilities.

A team led by Stephanie Wilkins, President, PharmaConsult US, presented "Risk Management and High Hazard Compounds" on 25 January to nearly 40 FDA personnel in Rockville, Maryland.

Lesley Burgess and Paul Wreglesworth of AstraZeneca, Nigel Hamilton of Sanofi-Aventis, Bruce Naumann and Ed Sargent of Merck, Andy Walsh of Hoffman-LaRoche, and Stephanie and Julian Wilkins of PharmaConsult US, demonstrated how a risk management approach can help define if and when certain products and processes need to be accommodated in dedicated or segregated facilities.

"The FDA approached us at the June 2005 ISPE Potent Compounds Containment Seminar and asked us to provide them with education on this topic," said Wilkins. "In general, the drugs in our industry are getting more and more potent, and so there is a concern for operator safety and cross-contamination."

"There is a trend heading toward separate production facilities, which would be traumatic to the industry, in terms of cost and time to market. Industry and regulators from around the world are struggling with this."

Last February, the European Agency for the Evaluation of Medicinal Products (EMEA) issued the "Concept Paper Dealing with the Need for Updated GMP Guidance Concerning Dedicated Manufacturing Facilities in the Manufacture of Certain Medicinal Products."

One of the proposals set out in this paper is that, "An expert agreement should be obtained when and for which 'certain' substances separate production buildings should be mandatory. At the same time, a definition of 'exceptional cases' should be given as to when production in campaigns may be acceptable in the same building."

Wilkins said industry leaders in the US and international organizations such as the European Federation of Pharmaceutical Industries and Associations (EFPIA) are concerned that the EMEA may be reinforcing the existing paradigm that high hazard substances immediately call for separate production facilities, when in fact, some of these substances can be processed safely in multi-product facilities.

"The 'exceptional cases' should be those where physical and procedural controls cannot show the ability to control potential cross-contamination to acceptable levels, which would require separation or dedication of facilities," Wilkins said. "Currently, we are basing decisions on a 'one size fits all' approach using product class, definitions, or labels, such as the emotion-provoking words, potent, cytotoxic, and cytostatic."

"We are a science-based industry, yet when it comes to discussing highly hazardous compounds, science goes out the window and we adopt an approach based on pure emotion!" said Wreglesworth.

"We need to reprogram ourselves to think in terms of hazard characterization and risk characterization when we consider compounds, Wilkins said. "These words take hazard classes like, carcinogens, mutagens, teratogens, and sensitizers into consideration, but also factor in differences of potency and actual level of exposure."

Further complicating the issue are the inconsistencies found in guidelines across the globe. For example, the Australian Code of cGMP for Medicinal Products issued in 2002 recommended that cross-contamination be avoided by "production in segregated areas . . . or by campaign (separation in time) followed by appropriate cleaning." In the same year, Health Canada proposed a modification to their guideline that addressed the same issue, but their view was that, "Campaign production (separation in time followed by cleaning) of the above products is not acceptable."

And in certain South American countries, cGMP inspections are conducted to a checklist based on the 1992 WHO guidance, which states, "Areas for preparation of pharmaceutical highly sensitizing products: penicillins, hormones, cytostatics, or biological preparations have to be independent and autonomous."

Currently, guidance on the quality risk management approach can be found in the ICH Q9 document proposed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. "But we need to take ICH Q9 a step further and develop a specific science- and risk-based approach to the process to determine whether certain products should be accommodated in dedicated or segregated facilities," Wilkins said.

The Risk Management approach presented to the FDA in January is a systematic process to identify hazards and understand risks to assist decision-making to implement appropriate controls. The key components are hazard characterization, risk characterization, exposure assessment, control of the risks, verification of performance, communication, and review.

The approach utilizes the basic scientific equation, Hazard (the potential for a substance to produce adverse effects)

"We're not looking to create a matrix," said Wilkins, "rather, we would like there to be a formal documented approach that examines issues that affect exposure and realistic solutions."

x Exposure (contact with the substance) = Risk (the probability that a substance will produce harm under specified conditions of exposure).

The approach should be applied to hazard and risk assessment, but the controls put in place should be determined on a case by case basis, according to the presentation to the FDA. "We're not looking to create a matrix," said Wilkins, "rather, we would like there to be a formal documented approach that examines issues that affect exposure and realistic solutions."

Wilkins said the team's goals are to continue dialogue with the FDA and develop ISPE guidance for the industry in the areas of Risk Assessment, Risk Management, and Facility Design for highly hazardous compounds and possibly for all compounds. The team also plans to provide an expanded version of its presentation to the FDA at a one-day session at ISPE's Annual Meeting in November.

In response to the EMEA's concept paper, EFPIA experts sent to the EMEA and the European Commission on 27 January, "EFPIA Proposed Guidance Document on Dedicated Manufacturing Facilities in the Manufacture of Certain Medicinal Products." The document demonstrates how the risk-based decision approach can be used to determine the potential risk of cross-contamination and the type of controls required. The EFPIA experts also proposed new wording to the current EU GMP Guide to reduce ambiguity and allow risk management principals to be applied. The EMEA is expected to discuss EFPIA's revised text in early March.

Wilkins and her team would like to see industry and regulators worldwide agree on consistency of approach to hazard and risk assessment, but flexibility of approach in controlling the risk. "We want everyone to be on the same playing field and on one that is based on good science," Wilkins said.

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05	Delaware Valley Chapter Education Series Week 2 of 6
06	Puerto Rico Chapter Commissioning & Qualification Program
11	Delaware Valley Chapter Student Poster Contest
12	Delaware Valley Chapter Education Series Week 3 of 6
13	New Jersey Chapter Cambrex Tour
19	Delaware Valley Chapter Education Series Week 4 of 6
19	Japan Affiliate Annual Meeting
20	Midwest Chapter Education and Vendor Day
24 - 26	2006 FDA CGMP China Training Program
24 - 27	**ISPE Copenhagen Conferences**
26	Delaware Valley Chapter Education Series Week 5 of 6
27 - 28	**ISPE Brisbane, Australia Training Courses**
28 - 29	India Affiliate 2006 Conference

May 2006

01 - 02	**ISPE Melbourne, Australia Training Courses**
03	Delaware Valley Chapter Education Series Week 6 of 6
04 - 05	**ISPE Wellington, New Zealand Training Courses**
08	Delaware Valley Chap 13th Annual Golf Outing
08 - 11	**ISPE Atlanta Classroom Training**
10	New Jersey Chapter Golf Outing
18	Puerto Rico Chapter Method & Product Transfer Program
22 - 25	**ISPE Amsterdam Training**
27	Puerto Rico Chapter Annual Golf Tournament

June 2006

05 - 08	**ISPE Washington Conferences**
14	Chesapeake Bay Area 2006 Summer Social
15	New Jersey Chapter Day and Multi-Tract Event
22	Greater LA Chapter Social Event
22	Midwest Chapter Golf Outing and Executive Panel Discussions
25 - 27	**2006 ISPE Singapore Conference**
27 - 29	**INTERPHEX Asia**
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Theme: Regulatory
Manuscripts due: 3 July 2006
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JANUARY/FEBRUARY 2007
Theme: Sterile Manufacturing Operations
Manuscripts Due: 3 Jan 2007
Publishes: 22 May 2007

MARCH/APRIL 2007
Theme: Automation
Manuscripts due: 2 Mar 2007
Publishes: 20 July 2007

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IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

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